Assessment of the Rate of Skip Metastasis to Neck Level IV in Patients With Clinically Node-Negative Neck Oral Cavity Squamous Cell Carcinoma
A Systematic Review and Meta-analysis

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IMPORTANCE The rate of skip metastasis to neck level IV in patients with clinically node-negative neck (cN0) oral cavity squamous cell carcinoma (OCSCC) remains controversial.

OBJECTIVE To provide a high level of evidence using a meta-analysis on the rate of skip metastasis to level IV in this subset of patients.

DATA SOURCES The Embase, PubMed, and Google Scholar databases were searched for articles published during the period of January 1, 1970, through December 31, 2017, using the following key terms: neck dissection, NO neck, squamous cell carcinoma, skip metastasis, radical neck dissection, lymph node management, neck metastasis, oral cavity cancer, and tongue cancer. Some terms were also used in combination, and the reference section of each article was searched for additional potentially relevant publications. Data were analyzed from January 8 through 11, 2018.

STUDY SELECTION Inclusion criteria were all cohorts, including from any randomized clinical trial, case-control study, case study, and case report; studies of patients with the histopathologic diagnosis of OCSCC; and studies that differentiated data between skip metastasis and sequential metastasis to neck level IV. Of the 115 articles retrieved from the literature, 11 retrospective studies and 2 prospective randomized clinical trials (n = 1359 patients) were included.

DATA EXTRACTION AND SYNTHESIS Meta-analysis of Observational Studies in Epidemiology guidelines were followed. Fixed-effects model and 95% CIs were estimated, and data of included studies were pooled using a fixed-effects model.

MAIN OUTCOMES AND MEASURES Overall proportion of neck involvement and the rate of level IV skip metastasis. Subgroup analysis for primary site and tumor staging.

RESULTS The rate of level IV involvement in patients with cN0 ranged between 0% and 11.40% with a fixed-effects model of 2.53% (95% CI, 1.64%-3.55%). The rate of skip metastasis ranged from 0% to 5.50% with a fixed-effects model of 0.50% (95% CI, 0.09%-1.11%). The rate of level IV skip metastasis did not increase significantly in cases that involved neck levels I through III. Tumor staging and primary site tumor did not significantly affect the rate of skip metastasis.

CONCLUSIONS AND RELEVANCE This meta-analysis showed very low rates of skip metastasis to neck level IV in patients diagnosed with cN0 OCSCC. Encountering an allegedly positive lymph node during neck dissection does not portend high rates of level IV involvement. Supraomohyoid neck dissection is therefore adequate for this subset of patients.

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The treatment of oral cavity squamous cell carcinoma (OCSCC) has changed considerably over the past few decades. The pendulum has swung from extensive and radical neck surgeries to modified and selective types of neck dissections (NDs). The term supraomohyoid neck dissection (SOHND) refers to the removal of lymph nodes contained in levels I through III of the neck and is currently referred to as a selective ND in levels I through III. This type of ND has been frequently used in the management of clinically node-negative neck (cN0) in OCSCC and provides similar control rates as more extensive forms of NDs. However, several studies have concluded that SOHND is inadequate in patients with OCSCC, owing to occult metastasis to neck level IV, and that this level should be routinely dissected. The designation of the neck level of skip metastasis, the involvement of neck level IV without the involvement of previous levels, in patients with OCSCC remains a matter of controversy. Advocates for including level IV in routine NDs claim that it minimizes neck recurrence and improves prognosis, while opponents remain doubtful of its survival benefit and further argue that it harbors added morbidity and longer surgical time.

The aim of this study is to conduct a meta-analysis of all relevant published literature to scrutinize the rate of skip metastasis to level IV in patients diagnosed with OCSCC without preoperative evidence of neck involvement.

Methods

Information Sources and Search Strategy

We performed a methodical and comprehensive search for all relevant articles in the English literature published between January 1970 and December 2017 by using the electronic databases Embase, PubMed, and Google Scholar to search the key terms neck dissection, NO neck, squamous cell carcinoma, skip metastasis, radical neck dissection, lymph node management, neck metastasis, oral cavity cancer, and tongue cancer. Some terms were also used in combination. The reference section of each article was searched for additional potentially relevant publications.

Study Eligibility Criteria

All studies that included patients who underwent an ND of at least levels I through IV and were judged clinically to be preoperatively free of lymph node metastasis were eligible for inclusion in this meta-analysis. The inclusion criteria for the study design were (1) any prospective or retrospective cohort, including from any randomized clinical trial, case-control study, case study, and case report; (2) a study population with the histopathologic diagnosis of OCSCC; and (3) studies that differentiated between true skip metastasis (metastasis solely at neck level IV) and sequential metastasis to neck level IV. Studies that involved mixed populations of NO and clinically node-positive (cN+) necks were included only if they enabled sequestration of data that pertained solely to the cN0 necks. Exclusion criteria were (1) studies on patients who had undergone preoperative radiotherapy and chemotherapy, (2) studies on recurrent tumors, and (3) studies that did not enable differentiation between data extracted from patients with cN+ and those with cNO necks.

Data Extraction

Information regarding study design, patient characteristics, primary tumor treatment, sample size, and average follow-up time was retrieved from the selected articles. Data were initially extracted and evaluated by the 2 principal investigators (A.W. and R.R.) and thereafter rechecked and confirmed by 3 other investigators (N.C., D.M.F., and G.H.). The distributions of the T category, extent of ND, subsite of the primary tumor, and nodal metastasis were recorded (Table 1). A skip metastasis was defined as a positive level IV node on final pathology without the involvement of higher levels (ie, levels I-III). A level IV nodal metastasis coexisting with nodes at other neck levels was assessed separately. Because most of the available studies were retrospective and observational, we followed the guidelines for meta-analysis of observational studies.

Statistical Analysis

Fixed-effects and random-effects meta-analyses of single proportions were used in conjunction with the inverse variance method to calculate the overall proportion. The Freeman-Tukey double arcsine transformation was implemented to calculate overall proportions. The Clopper-Pearson method (exact binomial) was used to calculate the CI for the individual study results. Result heterogeneity among the studies was quantified using the inconsistency index I², and a value higher than 75% was considered to be substantial heterogeneity. Statistical analysis was conducted using R statistical software (version 3.3.3, R Foundation).

Results

Study Selection

The search strategy identified 115 articles published from January 1, 1970, to December 31, 2017. These articles were selected and transferred into EndNote (Thomson Reuters), and duplicates were removed. The various phases of assessing the abstracts and reasons for exclusion from the meta-analysis are depicted in Figure 1. A total of 11 retrospective and 2 prospective randomized clinical studies that met our inclusion criteria, with a total of 1359 patients, were subsequently included in the meta-analysis (Table 1).

Key Points

Question What is the rate of skip metastasis to neck level IV in patients with clinically node-negative neck (cNO) oral cavity squamous cell carcinoma (OCSCC)?

Findings In this meta-analysis of 13 studies, the rate of skip metastasis to neck level IV in patients with cNO OCSCC was found to be extremely low. The overall rate of level IV involvement was between 0% and 11.4%.

Meaning Supraomohyoid neck dissection appears to be an adequate treatment for patients with cNO OCSCC.
Meta-analysis Results

The rate of involvement of level IV among the patients with cN0 was 0% to 11.40% with a fixed-effects model of 2.53% (95% CI, 1.64%-3.55%) (Figure 2A).5,9,10,12,13,15-22 According to results of the meta-analysis, the rate of skip metastasis was extremely low, ranging from 0% to 5.50% with a fixed-effects model of 0.50% (95% CI, 0.09%-1.11%) (Figure 2B).5,9,10,12,13,15-22 Various combinations of metastatic patterns with involvement of level IV were analyzed separately in subgroup analyses (Table 2).9,12,13,15-19,21,22 The rate of level IV metastasis did not increase significantly in cases that involved higher levels (ie, levels I-III) of the neck. In fact, the highest fixed-effect model was 0.04% (95% CI, 0%-0.63%) for involvement of levels I, II, and IV. All other fixed-effects models equaled 0% (95% CI, 0%-0.75%). A subgroup analysis according to T stage showed that level IV involvement was 0% (n = 401; 95% CI, 0%-0.63%) for stages I and II and 0% (n = 129; 95% CI, 0%-1.16%) for stages III and IV.

Categorization by oral cavity subsites revealed significant findings only on oral tongue primary lesions. The analysis included 8 studies with 590 patients. The rate of involvement of neck level IV was 0% to 11.40% with a fixed-effects model of 3.60% (95% CI, 2.09%-5.42%) (Figure 3).5,10,12,15,16,19,20,22

Discussion

Although it is well established that patients with OCSCC are at high risk for lymph node metastasis, the extent of nodal involvement for each neck level remains controversial.12 One of the main confounders is the heterogeneity of the study groups, which results in the lack of data stratification by T stages, subsites, and involvement of other neck levels. Another bias in many publications stems from combining the
skirt Metastasis in Patients With Clinically Node-Negative Neck Oral Cavity Squamous Cell Carcinoma

Original Investigation Research

Figure 2. Rate of Level IV Involvement and True Skip Metastasis in Preoperative Patients With Clinically Node-Negative Necks

**A** Rate of level IV involvement

| Source                  | Events | Total | Proportion, % | Favors No Involvement | Favors Involvement | Weight, % |
|-------------------------|--------|-------|---------------|-----------------------|-------------------|-----------|
| Khaffi et al,15 2001    | 1      | 17    | 5.88 (0.15-28.65) |                       |                   | 1.3       |
| Byers et al,10 1997     | 9      | 163   | 5.52 (2.56-10.22) |                       |                   | 12.0      |
| Balasubramanian et al,16 2012 | 1   | 52    | 3.85 (0.47-13.21) |                       |                   | 38.0      |
| Crean et al,13 2003     | 5      | 49    | 10.20 (3.40-22.23) |                       |                   | 3.6       |
| Feng et al,17 2014      | 6      | 190   | 3.16 (1.17-6.75)  |                       |                   | 14.0      |
| Mishra et al,18 2010    | 0      | 13    | 0.00 (0.00-24.71) |                       |                   | 1.0       |
| Vishak and Rohan,19 2014 | 2   | 57    | 3.51 (0.43-12.11) |                       |                   | 1.0       |
| Cariati et al,20 2018   | 10     | 88    | 11.36 (5.59-19.91) |                       |                   | 4.2       |
| Dias et al,12 2006      | 3      | 71    | 4.23 (0.88-11.86)  |                       |                   | 6.5       |
| Shah et al,5 1990       | 6      | 192   | 3.12 (1.16-6.68)  |                       |                   | 5.2       |
| Guo et al,21 2014       | 2      | 160   | 1.25 (0.15-4.44)  |                       |                   | 14.1      |
| Brazilian Head and Neck Cancer Study Group,9 1998 | 5 | 76 | 6.58 (2.17-14.69) |                       |                   | 11.8      |
| Aparwal et al,22 2018   | 0      | 231   | 0.00 (0.00-1.58)  |                       |                   | 5.6       |
| Fixed-effect model      | 1359   | 2.53 (1.64-3.55) |                       |                       | 100      |

**B** Rate of level IV true skip metastasis

| Source                  | Events | Total | Proportion, % | Favors No Involvement | Favors Involvement | Weight, % |
|-------------------------|--------|-------|---------------|-----------------------|-------------------|-----------|
| Khaffi et al,15 2001    | 0      | 17    | 0.00 (0.00-19.51) |                       |                   | 1.3       |
| Byers et al,10 1997     | 9      | 163   | 5.52 (2.56-10.22) |                       |                   | 12.0      |
| Balasubramanian et al,16 2012 | 1   | 52    | 3.92 (0.10-7.26)  |                       |                   | 38.0      |
| Crean et al,13 2003     | 2      | 49    | 4.08 (0.50-13.98) |                       |                   | 3.6       |
| Feng et al,17 2014      | 0      | 190   | 1.00 (0.00-1.92)  |                       |                   | 14.0      |
| Mishra et al,18 2010    | 0      | 13    | 0.00 (0.00-24.71) |                       |                   | 1.0       |
| Vishak and Rohan,19 2014 | 1   | 57    | 1.75 (0.04-9.39)  |                       |                   | 4.2       |
| Cariati et al,20 2018   | 1      | 88    | 1.14 (0.03-6.17)  |                       |                   | 6.5       |
| Dias et al,12 2006      | 1      | 71    | 1.41 (0.04-7.60)  |                       |                   | 5.2       |
| Shah et al,5 1990       | 3      | 192   | 1.56 (0.32-4.50)  |                       |                   | 14.1      |
| Guo et al,21 2014       | 0      | 160   | 0.00 (0.00-2.28)  |                       |                   | 11.8      |
| Brazilian Head and Neck Cancer Study Group,9 1998 | 2 | 76 | 2.63 (0.32-9.18) |                       |                   | 5.6       |
| Aparwal et al,22 2018   | 0      | 231   | 0.00 (0.00-1.58)  |                       |                   | 17.0      |
| Fixed-effect model      | 1359   | 0.50 (0.09-1.11) |                       |                       | 100      |

results of the primary neck surgery with those of revision surgeries for neck recurrences. These drawbacks became apparent during the process of data extraction, and they were addressed by excluding all patients with revision NDs and by omitting all groups lacking this information.

After performing a meta-analysis of all extracted data, we found that the actual rate of skip metastasis to level IV was only 0.5%. We also performed several subgroup analyses, the first of which was designed to account for the various primary tumor sites. Unfortunately, data in almost all of the analyzed articles failed to report the relations between the primary tumor site and the neck levels involved by metastatic tumor. Only primary lesions of the tongue could be accurately assessed. That analysis again confirmed a relatively low rate of skip metastasis, with a fixed-effects model of 3.60% (range, 0%-11.40%; 95% CI, 2.09%-5.42%). Another subgroup analysis was made on the various T stages. Once again, the majority of articles reviewed did not provide the rates of lymph node involvement according to the pathological T staging. Many articles did not differentiate between the various T stages or combined them into low (I-II) and high (III-IV) stages. Even so, the rate of the various T stages had relatively low influence on the rate of skip metastasis. Specifically, the rate of skip metastasis was 0% for advanced stage disease as well as for early stage disease, which was surprising considering that higher T stages are associated with infamously high rates of lymph node involvement. However, this figure probably represents a selection bias. Because only a small number of articles provided the correlation between T stages and skip metastasis, these articles shift the statistical analysis to manifest negligible level IV metastasis. On the same note, a recently published study on the Surveillance, Epidemiology, and End Results Program database did find a linear correlation between the initial T stage and neck involvement, including level IV, but did not differentiate patients deemed preoperative as clinically N0. This article also provided data on the relation between the
primary site tumor and neck metastasis. As for both parameters (T stage and primary site), neck level IV involvement did not exceed 11.2%, even for patients with a cN+ neck on presentation.

The idea of skip metastasis was initially described by Byers et al\textsuperscript{10} and refers to the condition in which OCSCC bypasses levels I, II, or both and goes directly to levels III or IV. Those authors reported a 15.8% rate of skip metastasis and therefore recommended routine dissection at neck level IV. Careful analysis of their data, however, revealed that only 5.5% of patients with clinical cN0 disease had skip metastasis to level IV in the initial ND specimen. Moreover, they described another 9 patients (9.9%) with recurrences at neck level IV, which had not been included in an earlier ND. Accounting for neck recurrence as a missed pathological lymph node in the primary surgery is problematic. The neck

### Table 2. Subgroup Analysis Showing Metastatic Patterns With Involvement of Level IV in Preoperative Patients With Clinically Node-Negative Necks

| Combination of Involved Neck Levels | Source | No. of Patients | Fixed-Effect Model (95% CI), % |
|-------------------------------------|--------|----------------|--------------------------------|
| I, II, III, IV                      | Khafif et al,\textsuperscript{15} 2001 | 384 | 0 (0-0.75) |
|                                     | Balasubramanian et al,\textsuperscript{16} 2012 | | |
|                                     | Mishra et al,\textsuperscript{18} 2010 | | |
|                                     | Dias et al,\textsuperscript{14} 2006 | | |
|                                     | Agarwal et al,\textsuperscript{22} 2018 | | |
| I, II, IV                           | Crean et al,\textsuperscript{13} 2003 | | |
|                                     | Feng et al,\textsuperscript{17} 2014 | | |
|                                     | Mishra et al,\textsuperscript{18} 2010 | 643 | 0.04 (0-0.63) |
|                                     | Guo et al,\textsuperscript{24} 2014 | | |
|                                     | Agarwal et al,\textsuperscript{22} 2018 | | |
| I, III, IV                          | Crean et al,\textsuperscript{13} 2003 | 293 | 0 (0-0.23) |
|                                     | Mishra et al,\textsuperscript{18} 2010 | | |
|                                     | Agarwal et al,\textsuperscript{22} 2018 | | |
| I, IV                               | Mishra et al,\textsuperscript{18} 2010 | | |
|                                     | Brazilian Head and Neck Cancer Study Group,\textsuperscript{9} 1998 | 320 | 0 (0-0.27) |
|                                     | Agarwal et al,\textsuperscript{22} 2018 | | |
| II, III, IV                         | Feng et al,\textsuperscript{17} 2014 | 491 | 0 (0-0.37) |
|                                     | Mishra,\textsuperscript{19} et al 2010 | | |
|                                     | Vishak and Rohan,\textsuperscript{19} 2014 | | |
|                                     | Agarwal et al,\textsuperscript{22} 2018 | | |
| II, IV                              | Feng et al,\textsuperscript{17} 2014 | 434 | 0 (0-0.35) |
|                                     | Mishra et al,\textsuperscript{18} 2010 | | |
|                                     | Agarwal et al,\textsuperscript{22} 2018 | | |
| III, IV                             | Crean et al,\textsuperscript{13} 2003 | | |
|                                     | Feng et al,\textsuperscript{17} 2014 | | |
|                                     | Mishra et al,\textsuperscript{18} 2010 | 643 | 0 (0-0.23) |
|                                     | Guo et al,\textsuperscript{24} 2014 | | |
|                                     | Agarwal et al,\textsuperscript{22} 2018 | | |

### Figure 3. Oral Tongue Primary: Rate of Level IV Involvement in Preoperative Patients With Clinically Node-Negative Necks

| Source                          | Events | Total | Proportion, % | Favors No Involvement | Favors Involvement | Weight, % |
|--------------------------------|--------|-------|---------------|-----------------------|--------------------|-----------|
| Khafif et al,\textsuperscript{15} 2001 | 1      | 17    | 5.88 (0.15-28.69) | | | 2.9 |
| Byers et al,\textsuperscript{10} 1997 | 9      | 163   | 5.52 (2.56-10.22) | | | 27.5 |
| Balasubramanian et al,\textsuperscript{16} 2012 | 2      | 52    | 3.85 (0.47-13.21) | | | 8.8 |
| Vishak and Rohan,\textsuperscript{19} 2014 | 2      | 57    | 3.51 (0.43-12.11) | | | 9.7 |
| Cariati et al,\textsuperscript{20} 2018 | 10     | 88    | 11.36 (5.59-19.91) | | | 14.9 |
| Dias et al,\textsuperscript{14} 2006 | 1      | 71    | 1.41 (0.04-7.60) | | | 12.0 |
| Shah et al,\textsuperscript{2} 1990 | 2      | 58    | 3.45 (0.42-11.91) | | | 9.8 |
| Agarwal et al,\textsuperscript{22} 2018 | 0      | 84    | 0.00 (0.00-4.30) | | | 14.2 |
| Fixed-effect model              | 590    | 590   | 3.60 (2.09-5.42) | | | 100 |

-0.05 -0.05 0.00 0.05 0.10 0.15 0.20 0.25 0.30 0.35 0.40 0.45 0.50 0.55 0.60 0.65 0.70 0.75 0.80 0.85 0.90 0.95 1.00

Level IV Involvement

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Conflicts of Interest Disclosures: None reported.

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Inclusion of Neck Level IV in Treatment of Patients With Clinically Node-Negative Oral Cavity Squamous Cell Cancer

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The extent of neck dissection (ND) for treatment of head and neck cancer has been an area of active research and changes in clinical practice for the last several decades. Radical NDs have largely been replaced by modified and selective NDs. The classic neck levels at risk for oral cavity cancers are levels I through III; elective dissection of these levels with a supraomohyoid neck dissection (SOHND) is recommended for many patients with clinical node-negative (cNO) oral cavity cancers given the risk of occult nodal disease. However, many authors, including Byers and colleagues, have suggested that SOHND is inadequate and that level IV should be included or at least described in the management of oral cavity subsites. The subgroup analysis of oral tongue cancers included oraltongue cancer patients while others included a variety of oral cavity subsites. The subgroup analysis of oral tongue cancers included 8 studies with 590 patients and showed that the risk of level IV involvement was higher than oral cavity cancer overall (3.60% vs 2.53%), although still less than 5%.

In performing their meta-analysis, Warshavsky and colleagues used appropriate methodology and reporting in compliance with accepted guidelines of Meta-analyses of Observational Studies in Epidemiology. Despite their rigorous methods, a key limitation is that not all of the studies included in the meta-analysis provided enough data for the subgroup analyses. For each combination of pathologically involved nodal levels, only 1 study was included in each of the subgroup analyses. Subsites that were included varied between studies, because some studies only included oral tongue cancers while others included a variety of oral cavity subsites. The subgroup analysis of oral tongue cancers included 8 studies with 590 patients and showed that the risk of level IV involvement was higher than oral cavity cancer overall (3.60% vs 2.53%), although still less than 5%.

Although the concept of skip metastasis in oral cancer has been discussed for decades and most head and neck surgeons have anecdotes of level IV involvement from their own patients, the meta-analysis by Warshavsky and colleagues shows that the risk of level IV involvement is less than 5%. For that reason, the authors conclude that elective treatment of level IV is not required in patients with cNO oral cavity cancer. However, in my clinical practice, there are 2 situations in which I would consider adding level IV to the standard SOHND. The first situation would be when there is gross macroscopic...