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WILEY
Management of N0 Neck in Early Oral Squamous Cell Carcinoma: A Systematic Review and Meta-analysis

Conner Massey, MD; Anbuselvan Dharmarajan, MBBS; Raveendhara R. Bannuru, MD, PhD; Elie Rebeiz MD ©

Objective: The role of elective neck dissection (END) in patients with stage I (T1N0) and II (T2N0) squamous cell carcinoma of the oral cavity remains a controversial topic. We investigate the need for END by establishing a true incidence of occult nodal disease as a function of T stage.

Data Sources: MEDLINE, Google Scholar, Scopus.

Review Methods: Studies were selected using a set of inclusion and exclusion criteria. Meta-analysis using a random-effects model was employed to generate an odds ratio (OR) comparing the incidence of occult metastasis between T1 and T2 tumors, as well as regional recurrence rates between patients receiving END versus observation.

Results: Thirty-nine publications comprising five randomized controlled trials and 34 retrospective studies were selected for inclusion, yielding over 4,300 patients for analysis. The overall incidence of occult nodal metastasis, weighted by study size, was found to be 23%. Patients with T2 tumors have a significantly higher odds of having occult nodal disease (OR: 2.6, 95% confidence interval [CI]: 2.0-3.4) over patients with T1 tumors. We also demonstrate that for patients who are observed, the odds of recurrence are significantly higher (OR: 4.18, 95% CI: 2.78-6.28) compared to those who undergo END, although statistically significant interstudy heterogeneity was observed.

Conclusions: END should be reserved for stage II tumors given the significantly higher rate of occult metastasis. Observation may be more appropriate for stage I cancers.

Key Words: Oral cavity, squamous cell carcinoma, occult nodal metastasis, clinical N0 neck, elective neck dissection.

Laryngoscope 00:1–15, 2018

INTRODUCTION

In 2017, an estimated 49,670 new cases of oral and oropharyngeal cancer will be diagnosed in the United States, with 9,700 deaths projected.1 Although oral and oropharyngeal cancers are sometimes grouped together for epidemiological purposes, they are two distinct subsites, behave differently, and should be considered separate disease entities. They have different risk factors, natural history, and prognosis.2 This review only addresses cancers of the oral cavity.

The oral cavity extends from the lip to the anterior surface of the tonsils, encompassing the buccal mucosa, alveolar ridge, retromolar trigones, hard palate, anterior two-thirds of the oral tongue, and floor of mouth.

Squamous cell carcinoma (SCC) is the most common cancer of the oral cavity, representing more than 95% of all cases.3 The oral cavity has rich lymphatic drainage, and regional nodal metastasis occurs early and consistently in oral SCC.4 Approximately 30% of patients present with nodal metastasis at diagnosis, except in lip and hard palate SCC where the incidence is lower.5 The superior cervical lymph node groups (levels 1–3) provide first-echelon lymphatic drainage. Inferior cervical lymph node groups (levels 4 and 5) are rarely involved in the absence of metastasis to the first-echelon group,6 although “skip” metastases is well documented.7

Although surgical excision usually results in control of oral SCC primary tumor, recurrence often occurs in cervical lymph nodes, which is the most important factor in the long-term prognosis of patients. Metastatic nodal disease reduces the survival by half, and the salvage rate is often poor.8,9

Pathologic staging remains the gold standard in assessing nodal metastasis after neck dissection. Examination of the neck by manual palpation may be inaccurate, resulting in a 20% to 56% false-positive rate and a 16% to 60% false-negative examination in a histologically proven SCC (occult nodal disease).10

Computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) increase the accuracy of detecting involved lymph nodes.11–13 Fluorodeoxyglucose-PET staging in head and
neck SCC (HNSCC) provides good positive and negative predictive values in determining nodal status, and the maximum standardized uptake value of the primary tumor is predictive of overall survival. Imaging, however, cannot reliably detect the presence of nodal micrometastasis. Ultrasound-guided fine-needle aspiration (FNA) cytology can detect occult metastasis with reported sensitivity and specificity as high as 73% and 100%, respectively, in some studies and 42% to 50% sensitivity in others. Experience of the operator and cytopathologist may account for these variations. A combination of sentinel node lymphoscintigraphy and ultrasound-guided FNA cytology was reported without significant improvement in cancer detection.

Sentinel lymph node biopsy (SLNB) is heralded as a sensitive diagnostic modality and potential alternative staging procedure to neck dissection due to its reduced morbidity. Studies found SLNB to be a valid diagnostic technique that correctly stages regional metastases in HNSCC. Mehta and Nathan found that SLNB is highly sensitive, cost-effective, and improves quality of life. Ferris et al. found that intraoperative detection of metastatic HNSCC using multiplexed quantitative real-time polymerase chain reaction (qRT-PCR) can be rapid, accurate, and may enable intraoperative use of SLNB for decision making. MicroRNA molecules, which are small noncoding RNA molecules, were found to be regulators of gene expression in several plants and animals and biomarkers for detecting cancer cells in saliva. They were found to be specific to metastatic nodes of HNSCC and to be accurate diagnostic markers of nodal metastases. This promising technique allows evaluation of FNA and biopsy specimens, reduces intraoperative sampling bias of sentinel lymph nodes, and provides follow-up by testing suspicious lymph nodes.

The role of elective neck dissection (END) in T3 and T4 tumors is clear: to improve regional control and regional recurrence-free survival, but when compared with observation of the neck it does not improve overall survival. END can also help accurately stage the disease in patients with N0 neck. However, the optimal management of a clinically negative (cN0) neck in T1 and T2 oral cavity SCC remains a topic of debate. The benefits of END remain uncertain, because many studies have aimed to determine the role of END in cN0 neck, but definitive evidence of its value is lacking. There is a paucity of good prospective data, and much of the existing literature represents retrospective series reflecting experience from a single institution.

To this end, we conducted a systematic review and meta-analysis analyzing evidence for managing cN0 in T1 and T2 oral cavity SCC. As many studies demonstrated conflicting evidence regarding the survival benefit of END over observation, we sought to address the following questions that might aid the surgeon in selecting optimal management: 1) The primary question is: what is the incidence of occult neck metastasis in T1N0 (stage I) and T2N0 (stage II) oral cavity SCC? 2) What is the incidence of occult neck metastases based on the T stage (T1 vs. T2) in cN0 patients? 3) What is the recurrence rate in cN0 neck patients receiving END as compared to those observed, and how many were surgically salvaged?

We hypothesized that occult neck metastasis in T1 and T2 HNSCC is greater than 20%; thus, END should be considered.

METHODS

Data Sources/Searches

We searched MEDLINE, Google Scholar, and Scopus from inception to June 2018 using the following words or phrases in various combinations: “oral cancer,” “neck dissection,” “elective,” “neck staging,” “clinically negative,” “cN0,” and “neoplasm staging.” No limits were applied for language, publication date, or publication status, and foreign language articles were translated. We also hand searched the reference lists of all relevant systematic reviews and meta-analyses.

Study Selection

Studies were selected based on the inclusion and exclusion criteria listed in Table I. Two reviewers (E.R., C.M.) independently screened articles and abstracts recovered by the search. Articles deemed potentially relevant were obtained and assessed in detail by each reviewer independently according to the above criteria. All discrepancies were resolved by consensus.

Data Extraction and Quality Assessment

Three reviewers (E.R., C.M., A.D.) independently extracted data from each study, which were reviewed for consistency among the reviewers, and any discrepancies were resolved by consensus. The following data were extracted from each study when possible: 1) country where the study was performed; 2) study center; 3) study design (randomized controlled trials [RCTs], retrospective case series); 4) site of primary tumor; 5) disease characteristics including verification of diagnosis, nodal status, staging definition; 6) clinical method used in evaluating the neck; 7) study exclusion criteria; 8) method used in managing the primary tumor; 9) type of neck dissection; 10) adjuvant treatment of the neck; and 11) outcomes.

Two independent reviewers (A.D., R.E.B.) assessed risk of bias for each study using the Cochrane risk of bias tool and Newcastle Ottawa Scale Score, with any discrepancies resolved by consensus. Level of evidence was assessed using Oxford Centre for Evidence-Based Medicine Levels of Evidence.

Outcome Definitions

Outcomes of interest were determined and defined a priori. There is some disagreement in the literature as to what constitutes occult nodal metastasis. A number of studies considered cN0 patients to have occult nodal disease if they underwent observation of the neck and later developed clinically detectable nodal disease. These patients were not included in our analysis of occult nodal metastasis.
metastasis incidence. Because the time frame for developing clinically detectable nodes was highly variable, it was impossible to determine whether nodal disease represented initial occult metastasis or new metastasis. Thus, patients who were observed and later developed nodal disease were considered to have recurrence rather than occult nodal disease. For each study, the incidence of occult nodal metastasis was calculated only with patients who were found to have pathologically confirmed nodal disease during END at the time of primary treatment.

Neck recurrence was defined as clinically detectable metastatic disease limited to the neck following END or observation, so patients who had recurrence at the primary site or had distant metastasis were excluded. Salvage rate was defined as the percentage of patients with neck recurrence who were disease free 12 months after salvage surgery.

**Statistical Analysis**

An event rate was calculated for occult metastasis, neck recurrence, and salvage rate. We calculated an odds ratio (OR) with a 95% confidence interval (CI) for the incidence of occult metastasis in T1 versus T2 tumors, and for the recurrence rates in patients who received END versus observation. Considering the clinical and methodological heterogeneity of the available data, we used a random-effects model (DerSimonian-Laird) to pool the event rates and ORs. Heterogeneity was quantified using the $I^2$ statistic. Publication bias was assessed using funnel plots and Egger test. Meta-analysis was performed using Comprehensive Meta-Analysis (Biostat, Englewood, NJ).

**RESULTS**

Thirty-nine studies met the inclusion criteria out of 1,745 potential articles (Fig. 1, Table II). Five sets of studies utilized overlapping institutional datasets. The studies by Hughes et al. in 1993, Shi et al. in 1999, Spiro et al. in 1986, and Shah et al. in 1984, culled data from the Memorial Sloan Kettering Cancer Center (MSKCC). The study by Hughes et al. appeared to provide the most comprehensive dataset, and the remaining studies associated with MSKCC were not used in calculating an overall occult nodal metastasis incidence. Smith et al. in 2004 and Ebrahimi et al. in 2012 used overlapping institutional data from a hospital in Australia. The article by Ebrahimi et al. was used for data analysis as it was inclusive of Smith et al.’s. Similarly, Dias et al. and Kligerman et al. used the same institutional data from a hospital in Brazil, with a reported 63% overlap. Kligerman et al. were included for data analysis, as theirs was of superior study design. Hao and Tsang in 2002 and Huang et al. in 2005 reported data from the same hospital in Taiwan. The review by Huang et al. was used for data analysis, as it was inclusive of Hao and Tsang’s. Finally, data reported by Yuen et al. in 1997, 1999, and 2009 were from the same hospital in China, with inclusion periods dating 1980 to 1994, 1991 to 1997, and 1996 to 2004, respectively. All three studies were included in the data analysis, as they were not felt to have significant overlap. With the exclusion of the redundant studies, the remaining qualifying studies consist of five RCTs and 28 retrospective studies including 4,366 patients available for analysis.

**Incidence of Occult Nodal Metastasis**

Thirty-nine studies assessed occult nodal metastasis in patients with cN0 T1 and T2 of oral SCC who underwent END (Table II), with five RCTs and 34 retrospective studies. The rate of occult metastasis in patients with cN0 ranged from 20.6% to 49% in the RCTs, and 7.3% to 39.2% in the retrospective series. The overall rate of occult metastasis weighted by study size is 23%.

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**Table I: List of Inclusion and Exclusion Criteria for Study Selection**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients of any age and sex who had stage I (T1N0M0) or II (T2N0M0) SCC of the oral cavity with verification of diagnosis.</td>
<td>Non-squamous cell cancers of the oral cavity.</td>
</tr>
<tr>
<td>The oral cavity is defined in accordance with the AJCC or UICC.</td>
<td>The primary tumor site is outside the boundaries of the oral cavity.</td>
</tr>
<tr>
<td>Use of TNM staging per AJCC or UICC guidelines.</td>
<td>Study patients had evidence of clinical nodal disease.</td>
</tr>
<tr>
<td>Study patients lacked a history of prior head and neck surgery, radiotherapy, or chemotherapy.</td>
<td>Study focus on laboratory application in head and neck cancer.</td>
</tr>
<tr>
<td>Study patients were absent of clinical nodal disease.</td>
<td></td>
</tr>
<tr>
<td>Occult lymph node metastasis is clearly defined as the presence of metastasis in the sampled lymph node of a clinically disease-free neck found at elective neck dissection.</td>
<td></td>
</tr>
<tr>
<td>The techniques of neck dissection are well defined.</td>
<td></td>
</tr>
<tr>
<td>Elective neck dissection is defined as a neck dissection in a patient without clinically detectable disease.</td>
<td></td>
</tr>
</tbody>
</table>

*Radical neck dissection involves the excision of the internal jugular vein and its associated fibrous, adipose, and lymphatic tissue, as well as the spinal accessory nerve and the sternocleidomastoid muscle. Modified radical neck dissection involves preservation of any of the spinal accessory nerve, the sternocleidomastoid muscle, or the internal jugular vein. Supraomohyoid neck dissection involves selective removal of the lymph nodes at levels 1, 2, and 3 with the preservation of spinal accessory nerve, the internal jugular vein, and the sternocleidomastoid muscle. AJCC = American Joint Committee on Cancer. UICC = Union Internationale Contre le Cancer.*
Fifteen studies reported cases of oral tongue cancer only, two studies were restricted to patients with floor of mouth (FOM) cancer, and one study included patients with buccal cancer only. The remaining studies consisted of two or more anatomical sites or unspecified site. The method of clinical nodal evaluation was not reported in 16 studies.

Several studies analyzed clinical and histologic parameters predicting occult tumor metastasis to the neck. Crissman et al. \(^48\) reported that the presence of nodular or vertical infiltration into the submucosa in T2 FOM lesions had a 44% incidence of nodal metastasis. Kligerman et al. \(^41\) and Lydiatt et al. \(^53\) reported a trend toward increased rate of occult nodal metastasis with increased tumor thickness. Yeh et al. \(^69\) demonstrated that patients with evidence of perineural and/or lympho-vascular invasion were more likely to harbor occult nodal disease.

Extracapsular spread (ECS), a poor prognostic sign that is more commonly seen in T3 and T4 lesions, was observed in 4% to 94% of patients with nonpalpable neck nodes in stages I and II SCC of the oral cavity.\(^{55,48,73}\) The studies by Feng et al. in 2014, \(^64\) Yuen et al. in 2009, \(^46\) and D’Cruz et al. in 2015\(^71\) all noted that ECS was seen in a larger proportion of patients who underwent therapeutic dissection compared to those who received END.

### Tumor Stage

Twenty-one studies reported the incidence of occult neck metastases as a function of T stage in oral SCC (Table III). The odds of having occult nodal disease at the time of the primary tumor diagnosis are 2.6 times greater overall for T2 tumors compared to T1 tumors, and was statistically significant (95% CI: 2.0-3.4) (Fig. 2). The only individual studies that reached statistical significance were the ones by Huang et al. in 2008, \(^43\) Ebrahimi et al. in 2012, \(^39\) Thiele et al. in 2012, \(^62\) and Mücke et al. in 2014, \(^65\) Dias et al. in 2001\(^40\) and Peng et al. in 2014\(^67\) reported results of T1 tumors, and Yu et al. 2006\(^68\) reported only T2 tumors; for these reasons these studies were excluded from the meta-analysis. Weighted average for occult metastatic incidence among T1 tumors was 11.5%, compared to 24.5% for T2 tumors. No publication bias was detected (\(P = .81\)) (Fig. 3A).

### Neck Recurrence and Salvage Rates

Table IV lists the studies that reported the rates of regional neck recurrence following END or observation. Fleming and Long in 1988\(^51\) and Kerrebijn et al. in 1999\(^54\) reported recurrence rates limited to patients who received either END or observation, respectively; therefore, both studies were excluded from statistical analysis. The odds of developing recurrent neck disease were 4.18 times more in the neck surveillance group versus the END group, and the result was statistically significant (95% CI: 2.78-6.28) (Fig. 4). However, there was significant heterogeneity among the studies assessing recurrence rates (\(I^2 = 64.1\%\), \(P < .001\)). All studies demonstrated a decreased rate of recurrence in patients who received END compared to those who underwent neck observation, except for the studies by Lydiatt et al.\(^53\) and Peng et al.\(^67\) Ten of the 16 studies demonstrated statistical significance. No publication bias was detected. (\(P = .81\)) (Fig. 3B).
TABLE II.
Summary of 37 Studies Reporting the Incidence of Occult Metastasis in Patients With Stage I and II Squamous Cell Carcinoma of the Oral Cavity Who Underwent Elective Neck Dissection

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Center</th>
<th>Tumor Site</th>
<th>No. of Patients</th>
<th>Preoperative Nodal Evaluation</th>
<th>Method of Neck Dissection</th>
<th>Overall Rate of Occult Neck Metastasis (%)</th>
<th>Comments</th>
<th>Risk of Bias</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vandenbrouck 1980 (RCT)</td>
<td>Villejuif, France, Tongue, FOM</td>
<td>39</td>
<td>Not stated</td>
<td>RND</td>
<td></td>
<td>49 (19/39)</td>
<td>Interstitial curie therapy of primary tumor, postoperative neck XRT for pN+</td>
<td>Moderate</td>
<td>1</td>
</tr>
<tr>
<td>Crissman 1980</td>
<td>Cincinnati, OH, FOM</td>
<td>25</td>
<td>Exam under anesthesia</td>
<td>RND</td>
<td>24</td>
<td>Surgical resection of primary tumor, postoperative neck management not stated</td>
<td>Moderate</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Bradfield 1983</td>
<td>Dallas, TX, USA, Tongue</td>
<td>100, 110</td>
<td>Not stated</td>
<td>RND</td>
<td>8</td>
<td>Surgical resection or interstitial radiotherapy of primary tumor, postoperative neck management not stated</td>
<td>Low</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Teichgraeb 1984</td>
<td>Atlanta, GA, USA Tongue, FOM</td>
<td>86</td>
<td>Not stated</td>
<td>RND, SOHND</td>
<td>16.3</td>
<td>Interstitial radiotherapy of primary tumor, postoperative neck XRT</td>
<td>Moderate</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Shaha 1984§</td>
<td>MSKCC, USA FOM</td>
<td>78</td>
<td>Not Stated</td>
<td>RND</td>
<td>17</td>
<td>Surgical resection of primary tumor, postoperative XRT for (+) margins and ECS</td>
<td>Low</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Cunningham 1986</td>
<td>Pittsburgh, PA, Tongue, FOM</td>
<td>52</td>
<td>Not Stated</td>
<td>MRND</td>
<td></td>
<td>Surgical resection of primary tumor, postoperative neck management not stated</td>
<td>Moderate</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Spiro 1986§</td>
<td>MSKCC, USA Tongue, FOM</td>
<td>29</td>
<td>Not stated</td>
<td>RND, MRND, SOHND</td>
<td>28</td>
<td>Surgical resection of primary tumor, postoperative neck XRT for pN+</td>
<td>Low</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Fleming 1988</td>
<td>Melbourne, Australia Tongue, FOM, alveolus, gingiva</td>
<td>76</td>
<td>Physical exam</td>
<td>SOHND</td>
<td>32.9</td>
<td>Surgery or radiation of primary, postoperative neck management not stated</td>
<td>Moderate</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Fakih 1989 (RCT)</td>
<td>Bombay, India Tongue</td>
<td>30</td>
<td>Not stated</td>
<td>RND</td>
<td>33.3</td>
<td>Surgical resection of primary tumor, postoperative XRT for positive margin and ECS</td>
<td>Moderate</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Shah 1990§</td>
<td>MSKCC, USA Tongue, FOM, RMT, hard palate, gingiva</td>
<td>295</td>
<td>Physical exam</td>
<td>RND</td>
<td>34</td>
<td>Surgery or radiation of primary tumor, postoperative neck management not stated</td>
<td>Moderate</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Hughes 1993§</td>
<td>MSKCC, USA Oral cavity: NOS</td>
<td>48</td>
<td>Not stated</td>
<td>RND</td>
<td>34</td>
<td>Surgical resection of primary tumor, postoperative neck management not stated</td>
<td>Low</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Lydiatt 1993</td>
<td>MDACC, USA Tongue</td>
<td>54</td>
<td>Not stated</td>
<td>Not specified</td>
<td>20.4</td>
<td>Surgical resection of primary tumor, postoperative neck management not stated</td>
<td>Low</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Kligerman 1994 (RCT)</td>
<td>Rio de Janeiro, Brazil Tongue, FOM</td>
<td>34</td>
<td>Not stated</td>
<td>SOHND</td>
<td>20.6</td>
<td>Surgical resection of primary tumor, postoperative neck XRT for pN+</td>
<td>High</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Yuen 1997</td>
<td>Hong Kong, China Tongue</td>
<td>33</td>
<td>Not stated</td>
<td>SOHND, MRND, RND</td>
<td>27</td>
<td>Surgical resection of primary tumor, postoperative neck XRT for pN+</td>
<td>Moderate</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

(Continues)
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Center</th>
<th>Tumor Site</th>
<th>No. of Patients</th>
<th>Preoperative Nodal Evaluation</th>
<th>Method of Neck Dissection</th>
<th>Overall Rate of Occult Neck Metastasis (%)</th>
<th>Comments</th>
<th>Risk of Bias</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kerrebijn 1999</td>
<td>Toronto, Canada</td>
<td>Oral cavity: NOS</td>
<td>37</td>
<td>Physical exam and CT or MRI</td>
<td>SOHND</td>
<td>18.9</td>
<td>Surgical resection of primary tumor, postoperative neck XRT for pN+ and/or ECS</td>
<td>Low</td>
<td>3</td>
</tr>
<tr>
<td>Yuen 1999</td>
<td>Hong Kong, China</td>
<td>Tongue</td>
<td>50</td>
<td>Not stated</td>
<td>SOHND, MRND, RND</td>
<td>36</td>
<td>Surgical resection of primary tumor, postoperative neck XRT for pN+</td>
<td>Moderate</td>
<td>3</td>
</tr>
<tr>
<td>Dias 2001</td>
<td>Rio de Janeiro, Brazil</td>
<td>Tongue, FOM</td>
<td>24</td>
<td>Not stated</td>
<td>SOHND</td>
<td>20.8</td>
<td>Surgical resection of primary tumor, postoperative neck XRT for pN+</td>
<td>Moderate</td>
<td>3</td>
</tr>
<tr>
<td>Kaya 2001</td>
<td>Ankara, Turkey</td>
<td>Tongue</td>
<td>46</td>
<td>Not stated</td>
<td>SOHND, MRND, RND</td>
<td>21.7</td>
<td>Surgical resection of primary; postoperative XRT or CRT, indications not stated</td>
<td>Moderate</td>
<td>3</td>
</tr>
<tr>
<td>Hao 2002§</td>
<td>Taoyuan, Taiwan</td>
<td>Tongue, FOM, RTM, buccal, hard palate, gingiva</td>
<td>101</td>
<td>Physical exam, and CT or MRI</td>
<td>SOHND, MRND</td>
<td>22.8</td>
<td>Surgical resection of primary tumor, postoperative XRT for pN+ or close margins; postoperative CRT for (+) margins, multiple pN+, ECS</td>
<td>Low</td>
<td>3</td>
</tr>
<tr>
<td>Smith 2004§</td>
<td>Sydney, Australia</td>
<td>Tongue, FOM, alveolus, RMT, buccal</td>
<td>75</td>
<td>Physical exam, CT or MRI</td>
<td>MRND, SOHND</td>
<td>36</td>
<td>Surgical resection of primary tumor, postoperative neck XRT indications not stated</td>
<td>Low</td>
<td>3</td>
</tr>
<tr>
<td>Keski-Säntti 2006</td>
<td>Helsinki, Finland</td>
<td>Tongue</td>
<td>44</td>
<td>Physical exam, CT, US, MRI</td>
<td>Not specified</td>
<td>34</td>
<td>Surgical resection ± concomitant XRT of primary tumor, postoperative neck management not stated</td>
<td>Low</td>
<td>3</td>
</tr>
<tr>
<td>Lim 2006</td>
<td>Seoul, South Korea</td>
<td>Tongue</td>
<td>54</td>
<td>Physical exam and CT or MRI</td>
<td>SOHND</td>
<td>28</td>
<td>Surgical resection of primary tumor; postoperative XRT for multiple pN+, ECS, (+) margins</td>
<td>Moderate</td>
<td>3</td>
</tr>
<tr>
<td>Yu 2006</td>
<td>Wuhan, China</td>
<td>Tongue, FOM, RMT, buccal, gingiva, hard palate</td>
<td>227</td>
<td>Physical exam and CT</td>
<td>SOHND, RND</td>
<td>25.6</td>
<td>T2 tumors only; surgical resection of primary; postoperative XRT for ECS, close margins, T3/T4 stage, PNI/LVI</td>
<td>Moderate</td>
<td>3</td>
</tr>
<tr>
<td>Zbären 2006</td>
<td>Bern, Switzerland</td>
<td>Tongue (60) FOM (30) NOS (10)</td>
<td>100</td>
<td>Not stated</td>
<td>SOHND</td>
<td>20</td>
<td>Surgical resection of primary tumor; postoperative neck XRT, indications not stated</td>
<td>Moderate</td>
<td>3</td>
</tr>
<tr>
<td>Huang 2008</td>
<td>Taoyuan, Taiwan</td>
<td>Tongue</td>
<td>324</td>
<td>Physical exam, and CT or MRI</td>
<td>SOHND, MRND</td>
<td>10.1</td>
<td>Surgical resection of primary tumor; postoperative XRT for pN+ or close margins; postoperative CRT for (+) margins, multiple pN+, ECS</td>
<td>Moderate</td>
<td>3</td>
</tr>
</tbody>
</table>

(Continues)
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Center</th>
<th>Tumor Site</th>
<th>No. of Patients</th>
<th>Preoperative Nodal Evaluation</th>
<th>Method of Neck Dissection</th>
<th>Overall Rate of Occult Neck Metastasis (%)</th>
<th>Comments</th>
<th>Risk of Bias</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>D’Cruz 2009</td>
<td>Mumbai, India</td>
<td>Tongue</td>
<td>159</td>
<td>Not stated</td>
<td>SOHND, MRND</td>
<td>20.1</td>
<td>Surgical resection of primary tumor; postoperative neck XRT for (+) margins, pN+, poor differentiation, PNI, T stage ≥3</td>
<td>Low</td>
<td>3</td>
</tr>
<tr>
<td>Yuen 2009 (RCT)</td>
<td>Hong Kong, China</td>
<td>Tongue</td>
<td>36</td>
<td>US and USgFNAC</td>
<td>SOHND</td>
<td>22</td>
<td>Surgical resection of primary tumor, postoperative neck XRT for pN+</td>
<td>Moderate</td>
<td>1</td>
</tr>
<tr>
<td>El-Naaj 2011</td>
<td>Haifa, Israel</td>
<td>Tongue, FOM, lip, gingiva, palate, buccal</td>
<td>68</td>
<td>Physical exam and CT</td>
<td>SOHND</td>
<td>16</td>
<td>Surgical resection of primary, postoperative XRT or CRT for pN + or close margins</td>
<td>Moderate</td>
<td>3</td>
</tr>
<tr>
<td>Ebrahimi 2012</td>
<td>Sydney, Australia</td>
<td>Tongue, FOM, alveolus, RMT, buccal</td>
<td>114</td>
<td>Physical exam, CT, or MRI</td>
<td>RND, MRND, SOHND</td>
<td>36.8</td>
<td>All primary tumors ≥ 4 mm thick, surgical resection of primary tumor ± postoperative neck XRT</td>
<td>Low</td>
<td>3</td>
</tr>
<tr>
<td>Thiele 2012</td>
<td>Heidelberg, Germany</td>
<td>Tongue, FOM, alveolus, buccal, maxilla</td>
<td>122</td>
<td>Physical exam, US, CT, MRI</td>
<td>SOHND</td>
<td>13.9</td>
<td>Surgical resection of primary tumor ± postoperative XRT/CRT, indications not given</td>
<td>Moderate</td>
<td>3</td>
</tr>
<tr>
<td>Flach 2013</td>
<td>Amsterdam, the Netherlands</td>
<td>Tongue, FOM</td>
<td>51</td>
<td>USgFNAC</td>
<td>RND, MRND, SOHND</td>
<td>39.2</td>
<td>Surgical resection of primary tumor; postoperative XRT for pN+, ECS, or delayed nodal metastasis</td>
<td>Moderate</td>
<td>3</td>
</tr>
<tr>
<td>Feng 2014</td>
<td>Beijing, China</td>
<td>Tongue</td>
<td>156</td>
<td>Physical exam and CT</td>
<td>RND, SOHND</td>
<td>25.6</td>
<td>Surgical resection of primary tumor, postoperative XRT for pN+</td>
<td>Moderate</td>
<td>3</td>
</tr>
<tr>
<td>Kelner 2014</td>
<td>Sao Paolo, Brazil</td>
<td>Tongue FOM</td>
<td>161</td>
<td>Physical exam + CT or MRI after 1990</td>
<td>RND, MRND, SOHND</td>
<td>21</td>
<td>Surgical resection of primary tumor; postoperative XRT for close margins, pN+, ECS, PNI</td>
<td>Moderate</td>
<td>3</td>
</tr>
<tr>
<td>Mücke 2014</td>
<td>Munich, Germany</td>
<td>Tongue</td>
<td>327</td>
<td>Physical exam, US, CT, MRI, tumor board</td>
<td>SOHND</td>
<td>18.6</td>
<td>Surgical resection of primary tumor, postoperative treatment of neck not stated</td>
<td>Moderate</td>
<td>3</td>
</tr>
<tr>
<td>Peng 2014</td>
<td>UCLA, USA</td>
<td>Tongue</td>
<td>88</td>
<td>Not stated</td>
<td>Not specified</td>
<td>23</td>
<td>T1 tumors only; surgical resection of primary tumor ± postoperative XRT or CRT, indications not stated</td>
<td>Low</td>
<td>3</td>
</tr>
<tr>
<td>Yang 2014</td>
<td>Nanjing, China</td>
<td>Maxillary alveolus, hard palate</td>
<td>51</td>
<td>Physical exam and CT</td>
<td>SOHND, MRND</td>
<td>9.8</td>
<td>Surgical resection of primary tumor; postoperative XRT for (+) margins or pN+, postoperative CRT for T4 status, ECS, neck level IV or V disease</td>
<td>Low</td>
<td>3</td>
</tr>
<tr>
<td>Yeh 2014</td>
<td>Taipei, Taiwan</td>
<td>Oral cavity: NOS</td>
<td>176</td>
<td>Physical exam and CT</td>
<td>Not specified</td>
<td>22.2</td>
<td>Surgical resection of primary tumor, postoperative XRT for (+) margins, pN2 disease, ECS</td>
<td>Low</td>
<td>3</td>
</tr>
</tbody>
</table>

(Continues)
TABLE II. Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Tumor Site</th>
<th>Method of Dissection</th>
<th>Overall Rate of Occult Nodal Metastasis (%)</th>
<th>Patients with Tumor Thickness ≤ 3 mm</th>
<th>Patients with Tumor Thickness &gt; 3 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOHND, MRND</td>
<td>7.3</td>
<td>Surgical resection of primary tumor, postoperative CRT for close margins, pN+; ECS, invasion depth ≥ 10 mm, UDS</td>
<td>Surgical perineural XRT for pN- ( ≥ 10 mm) Invasion, depth of invasion &gt; 10 mm</td>
<td>29.6</td>
<td>1.9%</td>
<td></td>
</tr>
<tr>
<td>D’Cruz et al.</td>
<td>243</td>
<td>Physical exam and US</td>
<td>SOHND</td>
<td>29.6</td>
<td>1.9%</td>
<td></td>
</tr>
<tr>
<td>D’Cruz 2015 (RCT)</td>
<td>151</td>
<td>Physical exam and CT</td>
<td>SOHND</td>
<td>29.6</td>
<td>1.9%</td>
<td></td>
</tr>
</tbody>
</table>

Patients who developed nodal metastasis in the setting of neck surveillance were excluded from analysis.

Denotes studies that were excluded from calculation of a weighted average due to overlap.

Denotes studies that had an insignificant number of patients with T3 disease that could not be excluded from analysis due to methods of reporting.

Risk of bias was assessed using Cochrane risk of bias tool for randomized controlled trials and New Castle Ottawa Scale for nonrandomized studies.

Level of evidence was assessed using Oxford Centre for Evidence-Based Medicine Levels of Evidence.

Denotes studies with primary results from clinical trials that had a significant number of patients with T3 disease that could not be excluded from analysis.

Several studies analyzed parameters influencing nodal recurrence. Kligerman et al. reported increased incidence of recurrent neck disease, with tumor thickness greater than 4 mm. Spiro et al. showed that patients with oral tongue and FOM tumors that were 2 mm or less in thickness had a neck recurrence rate of 1.9%, compared to 45.6% for patients whose primary lesions were thicker than 2 mm. D’Cruz et al. found tumor grade and perineural invasion to be independent risk factors of nodal recurrence. Ebrahimi et al. found an increased risk of neck recurrence in patients over the age of 65 years.

Five RCTs evaluated the value of END in early-stage oral SCC. The sample size in these studies ranged from 67 to 496 patients. In the study by Vandenbroucke et al., 75 patients with early-stage oral tongue and FOM SCC received treatment of their primary tumor with iridium-192 interstitial curie therapy. They were then randomized to either receive END or neck observation, followed by therapeutic neck dissection in subsequent presentation of nodal disease. There were three nodal recurrences (8%) in the END group and 19 nodal recurrences (52.8%) in the observation/therapeutic group, with no statistically significant difference in disease-free survival and overall survival.

Fakih et al. reported 70 patients with oral tongue SCC who underwent hemiglossectomy, and were randomized to either receive END or observation. There were nine nodal recurrences (30%) in the END group, and 23 nodal recurrences (57%) in the observation group. The disease-free survival rates for the elective and observation groups were 63% and 52%, respectively; however, the difference was not statistically significant.

In the study by Kligerman et al., 67 patients with oral tongue and FOM SCC were randomized to undergo resection of the primary tumor with either elective supraomohyoid neck dissection (SOHND) or observation of the neck. Of those who underwent resection alone, 33% had neck recurrence, whereas only 24% with SOHND had neck recurrence. The disease-free survival rates for the SOHND and observation groups were 72% and 49%, respectively, which was significantly different.

In a prospective randomized study, 71 patients with oral tongue SCC underwent elective SOHND (36 patients) or observation (35 patients) with primary tumor resection. Nodal recurrence occurred in 5.6% of patients who received END and 31.4% of patients in the observation arm. The 5-year disease-specific survival was 89% and 87% for the END and observation arm, respectively, which was not statistically significant.

The most recent and largest RCT to date was conducted by D’Cruz et al. in 2015. In this study, 496 patients were randomized to either receive END or observation. Nodal recurrence was found in a greater proportion of patients who underwent observation of the neck of 42.6% compared to 9.9% in the END group. The authors also found that there was no survival benefit with END in patients with tumors <3 mm in depth of invasion (DOI). The only significant predictor of node positivity in patients who underwent END was DOI, those with <3-mm and >3-mm DOI had 5.6% and 16.9% occult...
### TABLE III.
Summary of 21 Studies Reporting the Rate of Occult Neck Metastasis in Patients With T1 and T2 cN0 Oral Cavity Squamous Cell Carcinoma Who Underwent Elective Neck Dissection

<table>
<thead>
<tr>
<th>Study</th>
<th>Tumor Site</th>
<th>No. of Patients</th>
<th>Method of Neck Dissection</th>
<th>Occult Neck Metastasis Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T1</td>
</tr>
<tr>
<td>Bradfield 1983</td>
<td>Tongue</td>
<td>100</td>
<td>RND</td>
<td>4.5% (3/67)</td>
</tr>
<tr>
<td>Teichgraebner 1984</td>
<td>Tongue, FOM</td>
<td>86</td>
<td>RND, SOHND</td>
<td>6.4% (2/31)</td>
</tr>
<tr>
<td>Kligerman 1994 (RCT)</td>
<td>Tongue, FOM</td>
<td>34</td>
<td>SOHND</td>
<td>8% (3/37)</td>
</tr>
<tr>
<td>Kerrebijn 1999</td>
<td>Oral cavity: NOS</td>
<td>37</td>
<td>SOHND</td>
<td>18.2% (2/11)</td>
</tr>
<tr>
<td>Yuen 1999</td>
<td>Tongue</td>
<td>50</td>
<td>SOHND, MRND, RND</td>
<td>21% (4/19)</td>
</tr>
<tr>
<td>Dias 2001*</td>
<td>Tongue, FOM</td>
<td>24</td>
<td>SOHND</td>
<td>20.8% (5/24)</td>
</tr>
<tr>
<td>Kaya 2001</td>
<td>Tongue</td>
<td>46</td>
<td>SOHND, MRND, RND</td>
<td>19.3% (6/31)</td>
</tr>
<tr>
<td>Hao 2002*</td>
<td>Tongue, FOM, RTM, buccal, hard palate, gingiva</td>
<td>101</td>
<td>SOHND, MRND</td>
<td>26.5% (9/34)</td>
</tr>
<tr>
<td>Lim 2006</td>
<td>Tongue</td>
<td>54</td>
<td>SOHND</td>
<td>19% (5/28)</td>
</tr>
<tr>
<td>Yu 2006</td>
<td>Tongue, FOM, gingiva, RMT, buccal</td>
<td>227</td>
<td>SOHND, RND</td>
<td>–</td>
</tr>
<tr>
<td>Zbären 2006</td>
<td>Tongue, FOM, NOS</td>
<td>82</td>
<td>SOHND</td>
<td>14% (4/27)</td>
</tr>
<tr>
<td>Huang 2008</td>
<td>Tongue</td>
<td>324</td>
<td>SOHND, MRND</td>
<td>5.2% (8/153)</td>
</tr>
<tr>
<td>D’Cruz 2009</td>
<td>Tongue</td>
<td>159</td>
<td>SOHND, MRND</td>
<td>17.4% (12/69)</td>
</tr>
<tr>
<td>Ebrahimii 2012</td>
<td>Tongue, FOM, alveolus, RMT, buccal</td>
<td>114</td>
<td>RND, MRND, SOHND</td>
<td>19.4% (7/36)</td>
</tr>
<tr>
<td>Thiele 2012</td>
<td>Tongue, FOM, alveolus, buccal, maxilla</td>
<td>122</td>
<td>SOHND</td>
<td>5.9% (3/51)</td>
</tr>
<tr>
<td>Flach 2013</td>
<td>Tongue, FOM</td>
<td>51</td>
<td>RND, MRND, SOHND</td>
<td>0% (0/2)</td>
</tr>
<tr>
<td>Feng 2014</td>
<td>Tongue</td>
<td>156</td>
<td>RND, SOHND</td>
<td>18.0% (11/61)</td>
</tr>
<tr>
<td>Kelner 2014</td>
<td>Tongue, FOM</td>
<td>161</td>
<td>RND, MRND, SOHND</td>
<td>12.5% (4/33)</td>
</tr>
<tr>
<td>Mücke 2014</td>
<td>Tongue</td>
<td>327</td>
<td>SOHND</td>
<td>9.3% (18/193)</td>
</tr>
<tr>
<td>Peng 2014</td>
<td>Tongue</td>
<td>88</td>
<td>Not specified</td>
<td>23.0% (20/88)</td>
</tr>
<tr>
<td>Huang 2015</td>
<td>Buccal</td>
<td>151</td>
<td>SOHND, MRND</td>
<td>1.8% (1/57)</td>
</tr>
</tbody>
</table>

*Patients who developed nodal metastasis in the setting of neck surveillance were excluded from analysis.

*Study excluded from statistical analysis due to overlap.

FOM = floor of mouth; MRND = modified radical neck dissection; NOS = not otherwise specified; RCT = randomized controlled trial; RMT = retromolar trigone; RND = radical neck dissection; SOHND = supraomohyoid neck dissection.

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![Forest plot comparing incidence occult metastasis in T1 versus T2 oral cancer. CI = confidence interval.](http://www.laryngoscope.com)

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"Laryngoscope 00: 2018 Massey et al.: Oral SCC N0 Neck Elective Neck Dissection"
cervical metastases, respectively. The 3-year disease-free survival rates were 80% and 67.5% for the END and observation groups, respectively, which were statistically significant.

Overall, five RCTs including 760 patients have reported on disease-free survival. The odds of disease-free survival were 1.79 times more in the END group versus the neck surveillance group, and the result was not statistically significant (95% CI: 0.97-3.28) (Fig. 5). However, there was significant heterogeneity among the studies ($I^2 = 57\%$, $P < .001$). In a sensitivity analysis where an outlier study was removed from the analysis, the odds ratio became statistically significant (OR: 2.57, 95% CI: 1.86-3.55) with no heterogeneity among the studies ($I^2 = 0\%$).

Seven studies reported rates of surgical salvage of the neck following recurrence, which varied considerably, ranging from 0% to 100% for patients who underwent END, and from 27.3% to 100% for patients who were observed. Yuen et al. reported 100% successful surgical salvage in both treatment arms, although one patient in each arm eventually succumbed to distant metastasis.46 Statistical analysis was not used to compare salvage rates between END and neck surveillance given the limited number of studies and insubstantial number of patients.

**DISCUSSION**

In this article, the meta-analysis incorporated 39 studies spanning 4 decades examining the benefits of END versus observation in patients with early-stage oral SCC. One limitation of this study is that some articles included in the meta-analysis date back the 1980s. We
### TABLE IV.
Summary of Studies Reporting the Regional Recurrence Rate and Salvage Rate in cN0 T1 and T2 Squamous Cell Carcinoma of the Oral Cavity in Patients Treated With END Versus OBS

<table>
<thead>
<tr>
<th>Study</th>
<th>Tumor Site</th>
<th>No. of Patients</th>
<th>Method of Neck Dissection</th>
<th>Postoperative Neck Management</th>
<th>Neck Recurrence Rate</th>
<th>Salvage Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>END</td>
<td>OBS</td>
</tr>
<tr>
<td>Vandenbrouck</td>
<td>Tongue, FOM</td>
<td>75</td>
<td>RND</td>
<td>XRT to 55 Gy to the neck for pN+</td>
<td>8.0% (3/39)</td>
<td>52.8% (19/36)</td>
</tr>
<tr>
<td>1980 (RCT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cunningham 1986</td>
<td>Tongue, FOM</td>
<td>52</td>
<td>MRND</td>
<td>Not stated</td>
<td>0% (0/9)</td>
<td>42% (18/43)</td>
</tr>
<tr>
<td>Spiro 1986</td>
<td>Tongue, FOM</td>
<td>91</td>
<td>RND, MRND, SOHND</td>
<td>Not stated</td>
<td>3.4% (1/29)</td>
<td>27.0% (17/63)</td>
</tr>
<tr>
<td>Fleming 1988</td>
<td>Tongue, FOM, alveolus, gingival</td>
<td>226</td>
<td>SOHND</td>
<td>XRT not used</td>
<td>—</td>
<td>28.6% (43/150)</td>
</tr>
<tr>
<td>Fakih 1989 (RCT)</td>
<td>Tongue</td>
<td>70</td>
<td>RND</td>
<td>XRT for (+) surgical margin and perinodal infiltration</td>
<td>30% (9/30)</td>
<td>57% (23/40)</td>
</tr>
<tr>
<td>Lydiatt 1993</td>
<td>Tongue</td>
<td>156</td>
<td>Not specified</td>
<td>XRT for multiple pN+ and/or ECS</td>
<td>18.5% (10/54)</td>
<td>16.5% (17/102)</td>
</tr>
<tr>
<td>Kligerman 1994</td>
<td>Tongue</td>
<td>67</td>
<td>SOHND</td>
<td>XRT for pN+</td>
<td>11.8% (4/34)</td>
<td>33% (11/33)</td>
</tr>
<tr>
<td>(RCT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yuen 1997</td>
<td>Tongue</td>
<td>63</td>
<td>SOHND, MRND, RND</td>
<td>XRT to 60 Gy used with surgeon’s preference</td>
<td>9% (3/33)</td>
<td>47% (14/30)</td>
</tr>
<tr>
<td>Kerrebijn 1999</td>
<td>Oral cavity: NOS</td>
<td>43</td>
<td>SOHND</td>
<td>XRT for multiple pN+ and/or ECS</td>
<td>10.4% (5/48)</td>
<td>—</td>
</tr>
<tr>
<td>Smith 2004*</td>
<td>Tongue, FOM, RTM, buccal, alveolus</td>
<td>150</td>
<td>MRND, SOHND</td>
<td>XRT, indications of which are not stated</td>
<td>5.3% (4/75)</td>
<td>20% (15/75)</td>
</tr>
<tr>
<td>Keski-Säntti 2006</td>
<td>Tongue</td>
<td>80</td>
<td>Neck dissection NOS ± XRT, XRT alone</td>
<td>Not stated</td>
<td>9% (4/46)</td>
<td>24% (8/34)</td>
</tr>
<tr>
<td>Huang 2008</td>
<td>Tongue</td>
<td>380</td>
<td>MRND, SOHND</td>
<td>XRT for close margins, pN+; postoperative CRT for (+) margins, multiple pN+, ECS</td>
<td>12.3% (40/324)</td>
<td>28.6% (16/56)</td>
</tr>
<tr>
<td>D’Cruz 2009</td>
<td>Tongue</td>
<td>359</td>
<td>MRND, SOHND</td>
<td>XRT for (+) margins, pN+, poor differentiation, PNI, T stage ≥3</td>
<td>5.7% (9/159)</td>
<td>47% (94/200)</td>
</tr>
<tr>
<td>Yuen 2009 (RCT)</td>
<td>Tongue</td>
<td>71</td>
<td>SOHND</td>
<td>XRT for pN+</td>
<td>5.6% (2/36)</td>
<td>31.4% (11/35)</td>
</tr>
<tr>
<td>Ebrahimis 2012</td>
<td>Tongue, FOM, RTM, buccal, alveolus</td>
<td>153</td>
<td>RND, MRND, SOHND</td>
<td>XRT, indications of which are not stated</td>
<td>7% (8/114)</td>
<td>38.5% (15/39)</td>
</tr>
<tr>
<td>Feng 2014</td>
<td>Tongue</td>
<td>229</td>
<td>RND, SOHND</td>
<td>XRT for pN+</td>
<td>9.6% (15/156)</td>
<td>19.2% (4/73)</td>
</tr>
<tr>
<td>Kelner 2014</td>
<td>Tongue, FOM</td>
<td>222</td>
<td>RND, MRND, SOHND</td>
<td>XRT for close margins, pN+, ECS, PNI</td>
<td>6% (9/161)</td>
<td>8% (5/61)</td>
</tr>
<tr>
<td>Peng 2014</td>
<td>Tongue</td>
<td>123</td>
<td>Not specified</td>
<td>XRT or CRT, indications not stated</td>
<td>8.0% (7/88)</td>
<td>5.7% (2/35)</td>
</tr>
<tr>
<td>Yeh 2014</td>
<td>Oral cavity: NOS</td>
<td>253</td>
<td>Not specified</td>
<td>XRT for (+) margins, pN2 disease, ECS</td>
<td>9.1% (16/176)</td>
<td>24.7% (19/77)</td>
</tr>
</tbody>
</table>

(Continues)
feel, however, that the surgical techniques are still valid, and the data did not vary significantly in the last 4 decades. In fact, the literature continues to remain divided as to which therapy provides the greatest benefit to patients.

Furthermore, the fact that only five RCTs have been conducted over the years speaks to the difficulty of performing high-quality, unbiased investigations of this much-debated issue. Moreover, only two of the five studies were able to demonstrate statistically significant differences in survival between treatment arms. With this in mind, a different approach should be considered to address the question of how to manage the neck in these patients.

A analysis published by Weiss et al. argued that the decision to perform END in patients with clinically negative necks should be informed by the incidence of occult metastasis in these patients. The authors constructed a decision tree using a computer model comparing the outcomes following END, irradiation, or observation and performed analysis on the variable of the probability of occult metastasis with each strategy. They stated that if the true incidence of occult metastasis is greater than 20%, then cN0 patients should undergo END. They based this recommendation on an analysis of the utility of the management options, taking into account the incidence of node involvement, complications of treatment, and disease control rates. Our investigation demonstrated an overall occult nodal metastasis incidence of 23% for all stage I and II disease, which is greater than this threshold. However, it is considerably more revealing when the incidence of occult metastasis is subgrouped by tumor stage. Of the patients with T1 tumors, 11.5% had occult nodal disease, whereas patients with T2 tumors had over twice that incidence (24.5%). Our meta-analysis supports this finding, showing that the odds of harboring occult metastatic disease were 2.6 times greater for patients with T2 tumors compared to those with T1. These results argue for END to be restricted to patients with T2 disease given the significantly higher likelihood of occult metastasis. Although observation for neck metastasis may seem an appropriate option for patients with T1 tumors, 11.5% had occult nodal disease, whereas patients with T2 tumors had over twice that incidence (24.5%). Our meta-analysis supports this finding, showing that the odds of harboring occult metastatic disease were 2.6 times greater for patients with T2 tumors compared to those with T1. These results argue for END to be restricted to patients with T2 disease given the significantly higher likelihood of occult metastasis. Although observation for neck metastasis may seem an appropriate option for patients with T1 tumors, there is some strong evidence to suggest that DOI is an important factor in considering END. In fact, recent changes made to the TNM staging system in the 8th edition of the oral cavity staging of the American Joint Committee on Cancer reflects the importance of DOI and its negative effect on prognosis. In the new staging system, T1 is defined not only by the size of the primary tumor, but by DOI of <5 mm (T1: tumor ≤ 2 cm, ≤ 5 mm DOI). Therefore, the surgeon should carefully assess DOI, tailor surgical options, and individualize the need for adjunctive treatment including END based on these histologic findings.

In our review we also analyzed neck recurrence rates and salvage rates, given that control of the neck had been repeatedly linked to survival in patients with oral-cavity SCC. Our meta-analysis demonstrated that for patients who underwent END, the odds of developing neck recurrence were reduced by a factor of four compared to those who received neck surveillance. However, there was
significant heterogeneity among studies that cannot be easily explained. The first study reporting recurrence rates was published over 30 years ago, and diagnostic and treatment modalities have changed considerably since then. This era has seen the advent of advanced diagnostic imaging, including CT, MRI, and PET. Surgeons have largely abandoned radical neck dissection for these patients with early-stage disease, instead favoring SOHND, a staging procedure that avoids the morbidity associated with radical neck dissection while identifying patients who may need additional therapy.

It is also striking to see the immense interstudy variability with regard to postoperative treatment of the neck. Many studies simply did not report how the neck was managed in patients following surgery. Others reported that some patients received radiation to the neck or chemotherapy, but did not state the indications for these treatments. In those studies that did state the
indicators for postoperative radiation or chemotherapy, these indicators varied considerably, such as the presence of positive nodal disease, multiple positive nodes, ECS, poorly differentiated tumors, close or positive tumor margins, perineural invasion, or some combination of these findings.

The facts listed above may also in part explain the wide variation seen in surgical salvage rates. One would expect our ability to detect recurrent disease has improved over time with the addition of more sensitive diagnostics, and the data seem to reflect this to a degree. The RCT by Yuenet al. reported salvage rates of 100% in both treatment arms, which may be explained by the rigorous postoperative ultrasound surveillance protocol they utilized.

Because a great majority of the incorporated studies in our review were retrospective analyses, the conclusions derived above must be weighed against the limitations inherent to retrospective reviews. For patients in these studies, the decision of how to treat the neck was based on the clinical status of the patient and surgeon preference, and not randomization. Table III indicates that among patients who received END, the proportion of patients with T2 tumors was greater in the vast majority of the studies. It appears as though patients with T2 tumors were more likely to be selected for END rather than observation.

In this review we did not encounter any study assessing the risk of nodal metastasis in patients who are human papillomavirus (HPV) seropositive. This is probably due to the fact that cancer of the oral cavity is not as strongly associated with HPV as oropharyngeal cancer. In a study by Furniss et al. in 2007, the risk associated with HPV16 seropositivity was greatest for tumors of the pharynx (risk was 6.0) compared to the risk associated with tumors of the oral cavity (risk was 1.5). Furniss et al. found that 40.3% of patients with a tumor of the pharynx and 14.7% of those with a tumor of the oral cavity had positive serology compared to 10.7% of controls.

Another limitation of any such review is the propensity of different anatomical sites in the oral cavity to metastasize to the cervical nodes. Oral tongue and FOM had positive serology compared to 10.7% of controls. Furniss et al. found that 40.3% of patients with a tumor of the oral cavity (risk was 1.5). Furniss et al. found that 40.3% of patients with a tumor of the oral cavity (risk was 1.5). Furniss et al. found that 40.3% of patients with a tumor of the oropharynx and 14.7% of those with a tumor of the oral cavity (risk was 1.5). Furniss et al. found that 40.3% of patients with a tumor of the oropharynx and 14.7% of those with a tumor of the oral cavity (risk was 1.5).

The odds of having occult metastasis were significantly lower for patients with T1 tumors, and thus these patients would only receive limited benefit from END. Finally, our review demonstrated that END significantly reduced the rate of recurrence in the neck. Although more rigorous RCTs with larger study populations are still needed to determine the impact of END on disease-free survival, we hope that our findings will inform clinicians and surgeons on how to optimally manage these patients with early-stage SCC of the oral cavity.

BIBLIOGRAPHY


