The Laryngoscope

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

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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

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Editor's Note: This Manuscript was accepted for publication on September 26, 2018.

Accepted as a Triological Society Thesis (no. 2018-30).

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The authors have no funding, financial relationships, or conflicts of interest to disclose.

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DOI: 10.1002/lary.27627

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.[14,15] 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[16] and 42% to 50% sensitivity in others.[17–19] 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.[20]

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.[21] Studies found SLNB to be a valid diagnostic technique that correctly stages regional metastases in HNSCC.[22,23] Mehta and Nathan found that SLNB is highly sensitive, cost-effective, and improves quality of life.[23] 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.[21] MicroRNA molecules, which are small noncoding RNA molecules, were found to be regulators of gene expression in several plants and animals[24] and biomarkers for detecting cancer cells in saliva.[25–28] They were found to be specific to metastatic nodes of HNSCC[29] and to be accurate diagnostic markers of nodal metastases.[30] 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.R.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.[31]

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

TABLE I.
List of Inclusion and Exclusion Criteria for Study Selection

Inclusion Criteria	Exclusion Criteria
Patients of any age and sex who had stage I (T1N0M0) or II (T2N0M0) SCC of the oral cavity with verification of diagnosis.	Non–squamous cell cancers of the oral cavity.
30 or more patients in a study.	The primary tumor site is outside the boundaries of the oral cavity.
The oral cavity is defined in accordance with the AJCC or UICC.	Study patients had evidence of clinical nodal disease.
Use of TNM staging per AJCC or UICC guidelines.	Study focus on laboratory application in head and neck cancer.
Study patients lacked a history of prior head and neck surgery, radiotherapy, or chemotherapy.	
Study patients were absent of clinical nodal disease.	
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.	
The techniques of neck dissection are well defined.*	
Elective neck dissection is defined as a neck dissection in a patient without clinically detectable disease	

*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.

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)[32] to pool the event rates and ORs. Heterogeneity was quantified using the I^2 statistic.[33] 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,[34] Shah et al. in 1990,[35] Spiro et al. in 1986,[36] and Shaha et al. in 1984,[37] 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[38] and Ebrahimi et al. in 2012[39] 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.[38] Similarly, Dias et al.[40] and Kligerman et al.[41] 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[42] and Huang et al. in 2008[43] 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.[42] Finally, data reported by Yuen et al. in 1997,[44] 1999,[45] and 2009[46] 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[34–72] 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%.

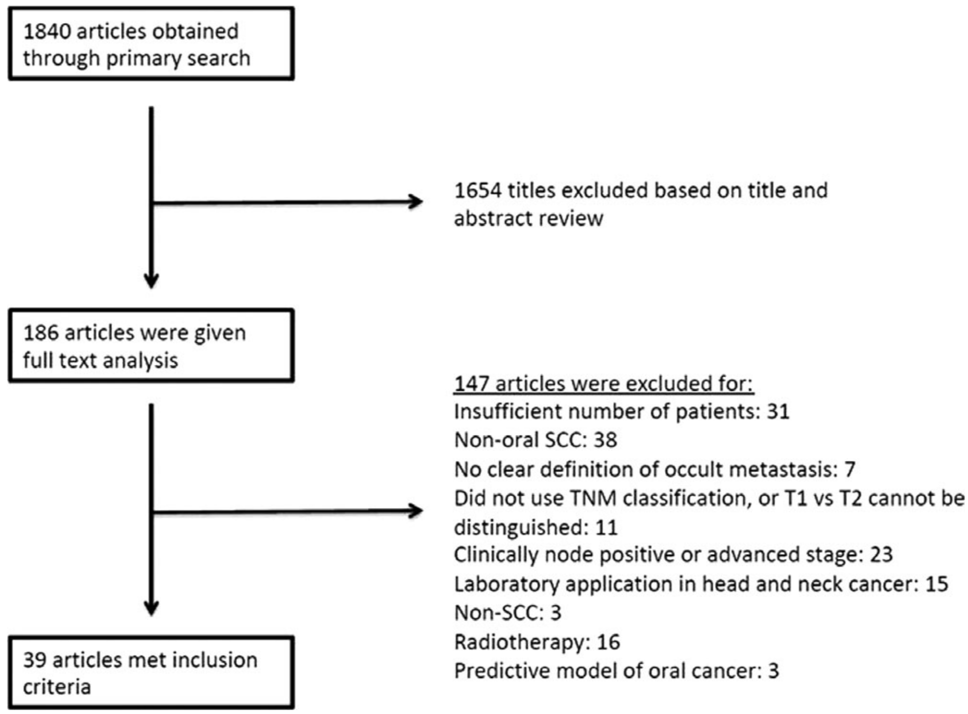


Fig. 1. Flow diagram illustrating the process of study selection. SCC = squamous cell carcinoma.

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 lymphovascular 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.[45,48,73] 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.[66] Dias et al. in 2001[40] and Peng et al. in 2014[67] reported results of T1 tumors, and Yu et al. 2006[58] 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

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

(Continues)

TABLE II.
Continued

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

(Continues)

TABLE II.
Continued

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

(Continues)

TABLE II.
Continued

Study	Study Center	Tumor Site	No. of Patients	Preoperative Nodal Evaluation	Method of Neck Dissection	Overall Rate of Occult Neck Metastasis (%)	Comments	Risk of Bias*	Level of Evidence†
Huang 2015	Taoyuan, Taiwan	Buccal	151	Physical exam and CT or MRI	SOHND, MRND	7.3	Surgical resection of primary tumor, postoperative XRT for close margins, pN+; postoperative CRT for poor differentiation, tumor depth ≥10 mm, ECS	Low	3
D'Cruz 2015 (RCT)	Mumbai, India	Tongue, FOM, buccal	243	Physical exam and US	SOHND	29.6	Surgical resection of primary tumor; postoperative XRT for pN+, (+) margins, depth of invasion >10 mm	High	2

*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 that had an insignificant number of patients with T3 disease that could not be excluded from analysis due to methods of reporting.
§Denotes studies that were excluded from calculation of a weighted average due to overlap.
||Patients who developed nodal metastasis in the setting of neck surveillance were excluded from analysis.
CRT = chemoradiation therapy; CT = computed tomography; ECS = extracapsular spread; FOM = floor of mouth; LVI = lymphovascular invasion; MDACC = M.D. Anderson Cancer Center; MRI = magnetic resonance imaging; MRND = modified radical neck dissection; MSKCC = Memorial Sloan-Kettering Cancer Center; NOS = not otherwise specified; pN + pathologically confirmed nodal metastasis; PNI = perineural invasion; RCT = randomized controlled trial; RMT = retromolar trigone; RND = radical neck dissection; SOHND = supraomohyoid neck dissection; UCLA = University of California, Los Angeles; US = ultrasound; USgFNAC = ultrasound-guided fine-needle aspiration cytology; XRT = radiotherapy.

Several studies analyzed parameters influencing nodal recurrence. Kligerman et al.[41] and Lydiatt et al.[53] reported increased incidence of recurrent neck disease, with tumor thickness greater than 4 mm. Spiro et al.[36] 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.[60] found tumor grade and perineural invasion to be independent risk factors of nodal recurrence. Ebrahimi et al.[39] 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 Vandenbrouck et al.,[47] 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.[52] 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.,[41] 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.[46] 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.[71] 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

Study	Tumor Site	No. of Patients	Method of Neck Dissection	Occult Neck Metastasis Rate	
				T1	T2
Bradfield 1983	Tongue	100	RND	4.5% (3/67)	11.6% (5/43)
Teichgraeber 1984	Tongue FOM	86	RND, SOHND	6.4% (2/31)	21.8% (12/55)
Kligerman 1994 (RCT)	Tongue, FOM	34	SOHND	8% (3/17)	12% (4/17)
Kerrebijn 1999	Oral cavity: NOS	37	SOHND	18.2% (2/11)	19.2% (5/26)
Yuen 1999	Tongue	50	SOHND, MRND, RND	21% (4/19)	45% (14/31)
Dias 2001*	Tongue, FOM	24	SOHND	20.8 (5/24)	—
Kaya 2001	Tongue	46	SOHND, MRND, RND	19.3% (6/31)	26.7% (4/15)
Hao 2002*	Tongue, FOM, RTM, buccal, hard palate, gingiva	101	SOHND, MRND	26.5% (9/34)	20.9% (14/67)
Lim 2006	Tongue	54	SOHND	19% (5/26)	36% (10/28)
Yu 2006	Tongue, FOM, gingiva, RMT, buccal	227	SOHND, RND	—	25.6% (58/227)
Zbären 2006	Tongue, FOM, NOS	82	SOHND	14% (4/27)	18% (10/55)
Huang 2008	Tongue	324	SOHND, MRND	5.2% (8/153)	14.6% (25/171)
D'Cruz 2009	Tongue	159	SOHND, MRND	17.4% (12/69)	22.2% (20/90)
Ebrahimi 2012	Tongue, FOM, alveolus, RMT, buccal	114	RND, MRND, SOHND	19.4% (7/36)	44.9% (35/78)
Thiele 2012	Tongue, FOM, alveolus, buccal, maxilla	122	SOHND	5.9% (3/51)	19.7% (14/71)
Flach 2013	Tongue, FOM	51	RND, MRND, SOHND	0% (0/2)	40.8% (20/49)
Feng 2014	Tongue	156	RND, SOHND	18.0% (11/61)	30.5% (29/95)
Kelner 2014	Tongue, FOM	161	RND, MRND, SOHND	12.5% (4/32)	22.5% (29/129)
Mücke 2014	Tongue	327	SOHND	9.3% (18/193)	32.1% (43/134)
Peng 2014	Tongue	88	Not specified	23.0% (20/88)	–
Huang 2015	Buccal	151	SOHND, MRND	1.8% (1/57)	10.6% (10/94)

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.

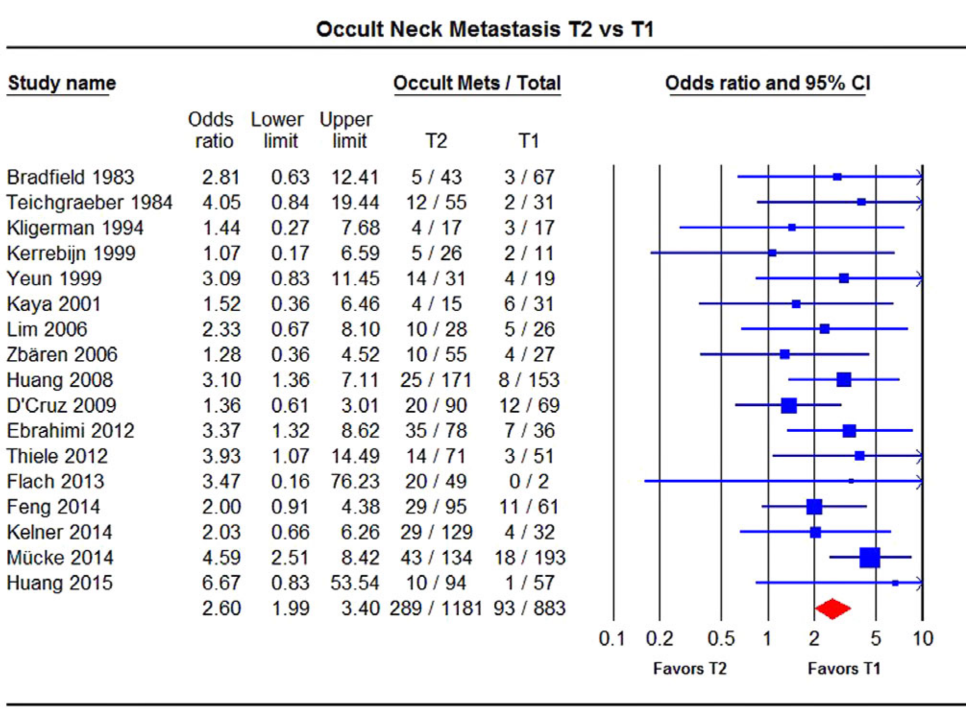


Fig. 2. Forest plot comparing incidence occult metastasis in T1 versus T2 oral cancer. CI = confidence interval. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

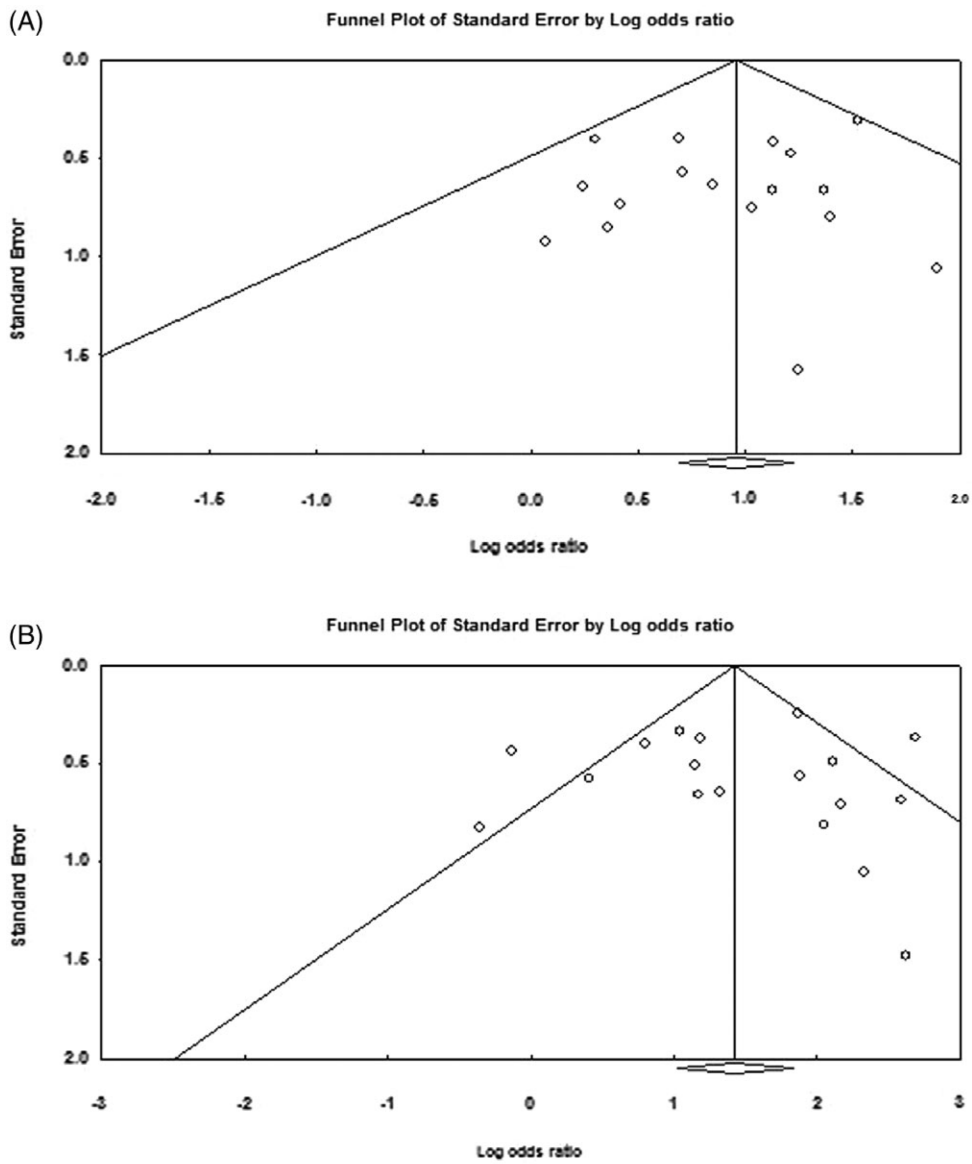


Fig. 3. (A) Funnel plot comparing incidence occult metastasis in T1 versus T2 oral cancer. (B) Funnel plot demonstrating neck nodal recurrence rates in patients undergoing observation versus elective neck dissection.

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

Study	Tumor Site	No. of Patients	Method of Neck Dissection	Postoperative Neck Management	Neck Recurrence Rate		Salvage Rate	
					END	OBS	END	OBS
Vandenbrouck 1980 (RCT)	Tongue, FOM	75	RND	XRT to 55 Gy to the neck for pN+	8.0% (3/39)	52.8% (19/36)	—	—
Cunningham 1986	Tongue, FOM	52	MRND	Not stated	0% (0/9)	42% (18/43)	—	—
Spiro 1986	Tongue, FOM	91	RND, MRND, SOHND	Not stated	3.4% (1/29)	27.0% (17/63)	—	—
Fleming 1988	Tongue, FOM, alveolus, gingival	226	SOHND	XRT is not used	—	28.6% (43/150)	—	—
Fakih 1989 (RCT)	Tongue	70	RND	XRT for (+) surgical margin and perinodal infiltration	30% (9/30)	57% (23/40)	22.2% (2/9)	30.4% (7/23)
Lydiatt 1993	Tongue	156	Not specified	XRT for multiple pN + and/or ECS	18.5% (10/54)	16.5% (17/102)	40% (4/10)	41% (7/17)
Kligerman 1994 (RCT)	Tongue, FOM	67	SOHND	XRT for pN+	11.8% (4/34)	33% (11/33)	25% (1/4)	27.3% (3/11)
Yuen 1997	Tongue	63	SOHND, MRND, RND	XRT to 60 Gy used with surgeon's preference	9% (3/33)	47% (14/30)	66% (2/3)	36% (5/14)
Kerrebijn 1999	Oral cavity: NOS	43	SOHND	XRT for multiple pN + and/or ECS	10.4% (5/48)	—	—	—
Smith 2004*	Tongue, FOM, RTM, buccal, alveolus	150	MRND, SOHND	XRT, indications of which are not stated	5.3% (4/75)	20% (15/75)	25% (1/4)	60% (9/15)
Keski-Säntti 2006	Tongue	80	Neck dissection NOS ± XRT, XRT alone	Not stated	9% (4/46)	24% (8/34)	—	—
Huang 2008	Tongue	380	MRND, SOHND	XRT for close margins, pN+; postoperative CRT for (+) margins, multiple pN+, ECS	12.3% (40/324)	28.6% (16/56)	—	—
D'Cruz 2009	Tongue	359	MRND, SOHND	XRT for (+) margins, pN+, poor differentiation, PNI, T stage ≥3	5.7% (9/159)	47% (94/200)	0% (0/9)	44% (41/94)
Yuen 2009 (RCT)	Tongue	71	SOHND	XRT for pN+	5.6% (2/36)	31.4% (11/35)	100% (2/2)	100% (11/11)
Ebrahimi 2012	Tongue, FOM, RMT, buccal, alveolus,	153	RND, MRND, SOHND	XRT, indications of which are not stated	7% (8/114)	38.5% (15/39)	—	—
Feng 2014	Tongue	229	RND, SOHND	XRT for pN+	9.6% (15/156)	19.2% (14/73)	46.7% (7/15)	35.7% (5/14)
Kelner 2014	Tongue, FOM	222	RND, MRND, SOHND	XRT for close margins, pN+, ECS, PNI	6% (9/161)	8% (5/61)	—	—
Peng 2014	Tongue	123	Not specified	± XRT or CRT, indications not stated	8.0% (7/88)	5.7% (2/35)	—	—
Yeh 2014	Oral cavity: NOS	253	Not specified	XRT for (+) margins, pN2 disease, ECS	9.1% (16/176)	24.7% (19/77)	—	—

(Continues)

TABLE IV.
Continued

Study	Tumor Site	No. of Patients	Method of Neck Dissection	Postoperative Neck Management	Neck Recurrence Rate		Salvage Rate	
					END	OBS	END	OBS
Huang 2015	Buccal	173	MRND, SOHND	XRT for close margins, pN+; postoperative CRT for poor differentiation, tumor depth ≥10 mm, ECS	6.6% (10/151)	31.8% (7/22)	—	—
D'Cruz 2015 (RCT)	Tongue, FOM, buccal	496	SOHND	XRT for pN+, (+) margins, tumor depth > 10 mm	9.9% (25/253)	42.6% (108/253)	—	—

The neck recurrence rate is defined as recurrence of disease in the neck only with the absence of recurrent disease elsewhere. Salvage rate is defined as the percentage of patients with recurrence in the neck that are disease free at 12 months follow-up after salvage surgery.

*Study excluded from statistical analysis due to overlap.

CRT = chemoradiation therapy; ECS = extracapsular spread; END = elective neck dissection; FOM = floor of mouth; MRND = modified radical neck dissection; NOS = not otherwise specified; OBS = observation; pN+ = pathologically confirmed nodal metastasis; PNI = perineural invasion; RCT = randomized controlled trial; RMT = retromolar trigone; RND = radical neck dissection; SOHND = supraomohyoid neck dissection; XRT = radiotherapy.

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.

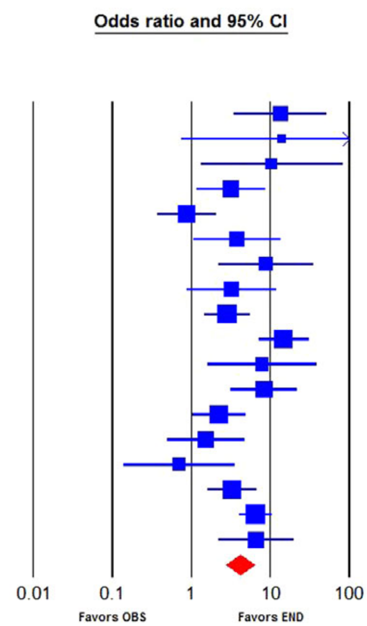
Furthermore, the fact that only five RCTs have been conducted over the years speaks to the difficulty of performing high-quality, unbiased investigations of this much-debated issue. Moreover, only two of the five studies were able to demonstrate statistically significant differences in survival between 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.[73] 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, there is some strong evidence to suggest that DOI is an important factor in considering END.[34,40,71] 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[74] 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

Recurrence Rate after OBS vs END

Study name	Odds ratio	Lower limit	Upper limit	Recurrence / Total OBS	Recurrence / Total END
Vandenbrouck 1980	13.41	3.49	51.60	19 / 36	3 / 39
Cunningham 1986	13.78	0.75	252.06	18 / 43	0 / 9
Spiro 1986	10.35	1.30	82.07	17 / 63	1 / 29
Fakih 1989	3.16	1.16	8.59	23 / 40	9 / 30
Lydiatt 1993	0.88	0.37	2.08	17 / 102	10 / 54
Kligerman 1994	3.75	1.05	13.35	11 / 33	4 / 34
Yuen 1997	8.75	2.19	35.02	14 / 30	3 / 33
Keski-Säntti 2006	3.23	0.88	11.81	8 / 34	4 / 46
Huang 2008	2.84	1.46	5.54	16 / 56	40 / 324
D'Cruz 2009	14.78	7.14	30.60	94 / 200	9 / 159
Yeun 2009	7.79	1.58	38.39	11 / 35	2 / 36
Ebrahimi 2012	8.28	3.15	21.75	15 / 39	8 / 114
Feng 2014	2.23	1.01	4.91	14 / 73	15 / 156
Kelner 2014	1.51	0.48	4.69	5 / 61	9 / 161
Peng 2014	0.70	0.14	3.55	2 / 35	7 / 88
Yeh 2014	3.28	1.58	6.80	19 / 77	16 / 176
D'Cruz 2015	6.49	4.01	10.53	108 / 253	25 / 243
Huang 2015	6.58	2.18	19.82	7 / 22	10 / 151
	4.18	2.78	6.28	418 / 1232	175 / 1882



Heterogeniety: I^2 = 65%

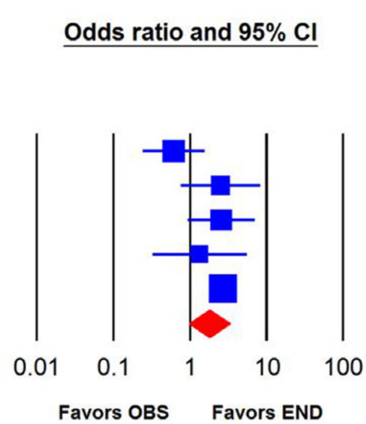
Fig. 4. Forest plot demonstrating neck nodal recurrence rates in patients undergoing observation (OBS) versus elective neck dissection (END). CI = confidence interval. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

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

Disease-Free Survival After OBS vs END

Study name	Odds ratio	Lower limit	Upper limit
Vandenbrouck 1980	0.61	0.25	1.53
Fakih 1989	2.50	0.76	8.19
Kligerman 1994	2.55	0.93	6.97
Yeun 2009	1.33	0.33	5.44
D'Cruz 2015	2.70	1.87	3.90
	1.79	0.97	3.28



Heterogeniety: I^2 = 57%

Fig. 5. Forest plot of surgical salvage rates in patients undergoing observation (OBS) versus elective neck dissection (END). CI = confidence interval. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

indications for postoperative radiation or chemotherapy, these indications 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.[46] 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,[75] 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 cancers were by far the most common sites represented here and are believed to have a higher incidence of nodal metastasis than those of the less common sites. It was impossible to perform a subgroup analysis of occult nodal metastasis for each anatomical site, as most studies did not specify subsites. Thus, it is unclear whether our results can be extrapolated to patients with lesions occurring in the less common sites.

CONCLUSION

Although the literature remains divided with regard to survival benefits of electively treating the neck, we opted to use an approach that was guided by the probability of patients with early-stage oral SCC to have occult metastatic disease. Among patients with stage I and II oral SCC, our results seem to support the need for END in patients with T2 SCC of the oral cavity given the high incidence of occult nodal metastasis in this population. 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.

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