Elective Neck Dissection Versus Observation in Squamous Cell Carcinoma of Oral Cavity With Clinically N0 Neck: A Systematic Review and Meta-Analysis of Prospective Studies

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Purpose: To assess the possible benefits of elective neck dissection (END) in patients with squamous cell carcinoma (SCC) of the oral cavity and clinically N0 neck.

Materials and Methods: Medline, Embase, the China National Knowledge Infrastructure, and the Wan Fang Database were systematically searched. A meta-analysis was performed to evaluate the possible benefits of END to such patients.

Results: Six prospective studies involving 865 patients fulfilled the inclusion criteria. Meta-analysis of all included studies showed that END substantially lowered the risk of regional recurrences (risk ratio [RR] = 0.27; 95% confidence interval [CI], 0.21-0.36) in the fixed-effect model compared with observation only. Three of the 6 included studies showed that the specific death rate related to regional recurrences was lower in the END group than in the observation group in the fixed-effect model (RR = 0.35; 95% CI, 0.19-0.65). The mean metastasis rate of occult cervical lymph node was 30.27% (standard deviation,

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9.42%). When the fixed-effect model was applied, 4 of the 6 included studies showed less recurrence in the END group compared with the observation group (RR = 0.53; 95% CI, 0.44-0.64).

Conclusions: END substantially decreases recurrences and deaths related to regional recurrences in early-stage SCC of the oral cavity with clinically N0 neck, especially SCC of the oral tongue and floor of the mouth, which is necessary for such patients.

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The oral cavity is 1 of the 10 most common locations in which malignant tumors arise, and it hosts a large proportion of head and neck cancers. Furthermore, more than 90% of these cancers are squamous cell carcinoma (SCC).[1] Cervical lymph node metastasis is a main reason of treatment failure, which considerably decreases the survival rate.[2,3] There is a consensus that neck dissection must be considered when apparent node metastasis is clinically found.[4] However, in early-stage SCC of the oral cavity, elective management of the clinically N0 neck has been a challenge and controversial during the past several decades.[5-7] Some researchers and clinicians believe that elective neck dissection (END) could avoid regional recurrences,[8,9] whereas others consider END an aggressive regime because of complications (eg, shoulder dysfunction, pain, and contour changes). Thus, an observation policy is preferred and recommended.[10-12]

Metastasis of cervical lymph nodes can occur at the early stage of SCC because lymphoid tissue in the head and neck region, especially the oral cavity, functions as a network.[1,6] Occult lymphatic metastasis of 25 to 46% in early-stage SCC of the oral cavity has been reported.[8,13-15] However, it is difficult to make a definite diagnosis of occult lymphatic metastasis because of the low sensitivity (75%) and general specificity (81%) of clinical examination of affected lymph nodes.[16] Although there are many modern imaging technologies, including ultrasonography, computed tomography, magnetic resonance imaging, and positron emission tomographic computed tomography, the sensitivity in detecting such occult metastases of the cervical lymph node is not satisfying.[17] Therefore, it is urgent to assess the necessity of END for patients with early-stage oral SCC and clinically N0 neck.

The authors systematically reviewed all existing prospective studies and carried out a meta-analysis. Five randomized controlled trials (RCTs) and 1 prospective matched case-and-control study were selected for the study. A total sample of more than 800 patients was included to compare END with observation or therapeutic neck dissection (TND) specifically in patients with early-stage oral SCC and clinically N0 neck to explore the potential benefits of END. A more rational treatment strategy acquired from such a work could yield a better reference for surgeons.

Materials and Methods

Because of the review nature of this study, it was granted an exemption in writing by the institutional review board of the West China Hospital of Stomatology of Sichuan University (Chengdu, China).

DATA SOURCES AND SELECTION CRITERIA

Medline through OVID (1946 to week 4 in November 2017), Embase through OVID (1974 to December 1, 2017), the China National Knowledge Infrastructure (1994 to 2017), and the Wan Fang Database (1984 to 2017) were systematically searched. There were no restrictions regarding language or date of publication, but the full text had to be available. Search terms were *tongue*, *lingua*, *gingival*, *gum*, *cheek*, *bucca*, *palatal*, *palate*, *floor of mouth*, *retromolar region*, *lip*, *labia*, *mouth*, *oral*, *cancer*, *carcinoma*, *neoplasm*, *tumor*, *tumour*, *squamous cell carcinoma*, *SCC*, *neck dissection*, and *cervical lymphadenectomy*.

All prospective studies comparing END with observation or TND were included in this systematic review for further meta-analysis. All patients had pathologically confirmed SCC of the oral cavity without clinically apparent metastasis of the cervical lymph node or distant metastases at the time of diagnosis. In addition, patients had not received previous antitumor treatment. Management for the primary tumor was surgery or radiotherapy. Close observation was offered to patients with clinically N0 neck, and TND was performed only when cervical lymph node metastasis was confirmed or strongly suspected. Minimum follow-up was 9 months.

Studies were excluded if the outcomes of interest were not available or not well defined. Two reviewers independently searched and assessed abstracts and full texts. Disagreements were resolved by consensus.

QUALITY ASSESSMENT

A Risk of Bias table recommended by the Cochrane Handbook for Systematic Reviews of Interventions (www.cochrane-handbook.org) was used to assess

the quality of included studies; the table includes 7 aspects of risk of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Each aspect was rated as having a low, high, or unclear risk of bias. Studies were assessed by 2 independent reviewers using the Risk of Bias table. Any disagreement was resolved by discussion.

DATA EXTRACTION

Information on study design, year of accrual, sample size, patient characteristics (age and gender), tumor site, tumor stage distribution, primary tumor treatment, and follow-up time was extracted (Tables 1,2). In addition, data of all outcomes were extracted. The first reviewer extracted these data from the original published work and imported them into predesigned data forms. The second reviewer checked the extracted data. Then, the 2 reviewers discussed any difference in opinion, and agreements were achieved by consensus. Four parameters were chosen as endpoints for the systematic review and meta-analysis: regional recurrences (cervical lymph node metastasis), specific death rate related to regional recurrences, occult cervical lymph node metastasis, and total number of recurrences (Table 3). The first 2 parameters were regarded as primary outcomes. An attempt was made to contact the investigators for relevant information that was not stated or not clear.

STATISTICAL ANALYSIS

Statistical analysis was performed using RevMan 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014). Risk ratios (RRs) of regional recurrences, specific death rate related to regional recurrences, and total number of recurrences were calculated with respective 95% confidence intervals (CIs) for each study. Specific death related to regional recurrences was defined as death from diseases (metastasis or recurrence) of the cervical lymph node, and the total number of recurrences was defined as any recurrence (eg, local recurrence, regional recurrence, and distant metastasis).

The level of statistical heterogeneity among the included studies was determined by χ^2-distributed Q statistic and I^2 statistic, and a P value less than .05 was defined as statistically significant. When heterogeneity was low ($P > .05$; $I^2 < 50\%$), a fixed-effect model was used; when heterogeneity was high ($P < .05$; $I^2 > 50\%$), a random-effect model was used. Forest plots were used to display the results of all outcomes. Publication biases were assessed by the Begg and Egger tests, and sensitivity analyses were performed using STATA 12.0 (StataCorp, College Station TX).

Results

LITERATURE SEARCH RESULTS

The search strategy yielded 5,638 articles from the Medline and Embase databases and 66 articles from the Chinese databases after removal of duplicates. Six prospective studies (5 RCTs and 1 prospective randomized matched case-and-control study) satisfied the inclusion criteria (Fig 1).[18-23] Analysis included 865 patients. The studies were single-center studies except for the study by Yuen et al.[23]

Table 1. CHARACTERISTICS OF INCLUDED STUDIES (PART 1)

Study	Design	Year of Accrual	Sample Size, N	Age (yr)	Male/ Female	Site
Mirea et al,[18] 2014 (Romania)	Prospective randomized matched case-and-control study	2000.1-2005.1	86	Mean 54	69/17	AT
Fakih et al,[19] 1989 (India)	Prospective randomized trial	1985.7-1988.9	70	NA	45/25	AT
Vandenbrouck et al,[20] 1980 (France)	Randomized trial	1966.12-1973.7	75	Mean 57	67/8	AT, FM
Kligerman et al,[21] 1994 (Brazil)	Prospective randomized study	1987-1992	67	Median 57	52/15	AT, FM
D'Cruz et al,[22] 2015 (India)	Prospective randomized, controlled trial	2004.1-2014.6	496	Mean 48	374/122	AT, BM, FM
Yuen et al,[23] 2009 (Hong Kong)	Prospective randomized study	1996-2004	71	Mean 57	43/28	AT

Abbreviations: AT, oral tongue (anterior two thirds of tongue); BM, buccal mucosa; FM, floor of mouth; NA, not available.

Table 2. CHARACTERISTICS OF INCLUDED STUDIES (PART 2)

Study	Tumor Stage Distribution (T1/T2/T3)	Stratification	Lymph Node Examination	Primary Tumor Treatment	Follow-Up Time (mo)
Mirea et al,[18] 2014 (Romania)	SND^+ 20/28; SND^- NA	Age and gender	Palpation, CT	Operation	Mean 90.5
Fakih et al,[19] 1989 (India)	24/46	No	NA	Operation	Median 20
Vandenbrouck et al,[20] 1980 (France)	15/48/10	No	NA	Radiotherapy	60
Kligerman et al,[21] 1994 (Brazil)	31/36	Stage	NA	Operation	42
D'Cruz et al,[22] 2015 (India)	219/277	Tumor site, stage, gender, and ultrasound findings	Physical examination, ultrasound	Operation	Median 39
Yuen et al,[23] 2009 (Hong Kong)	43/28	Stage	Clinical examination, ultrasound, aspiration	Operation	Mean 86

Abbreviations: CT, computed tomography; NA, not available; SND^-, without selective neck dissection; SND^+, with selective neck dissection.

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METHODOLOGIC QUALITY

The quality of each study was assessed by the Risk of Bias table. Evaluations are presented in Table 4. In the review of the 7 aspects of bias, studies by Vandenbrouck et al,[20] D'Cruz et al,[22] and Yuen et al[23] showed a relatively higher design quality, and the design quality of the other 3 studies was moderate.

REGIONAL RECURRENCES

All 6 studies reported outcomes of regional recurrences. All reported that regional recurrences in the END group were markedly decreased than in the observation and TND groups. The heterogeneity level of regional recurrences across studies was low (I^2 = 19%; P = .29); therefore, a fixed-effect model was used. Further, meta-analysis showed that END considerably lowered the risk of regional recurrences (RR = 0.27; 95% CI, 0.21-0.36; Fig 2A). There was no publication bias for this outcome ($Pr > |z| = .260 > .05$; $P > |t| = .534 > .05$). Sensitivity analysis indicated that the results were relatively stable (Fig 2B).

SPECIFIC DEATH RATE RELATED TO REGIONAL RECURRENCES

Four studies reported the specific death rate related to regional recurrences; however, only 3 studies could be synthesized for analysis. Compared with the observation or TND group, the END group showed lower specific death rates related to regional recurrences. Only 1 study by Mirea et al[18] reported statistical relevance. Data from the 3 studies had minimal heterogeneity (I^2 = 0%; P = .45) and were analyzed by a fixed-effect model (RR = 0.35; 95% CI, 0.19-0.65). The 3 studies yielded relevant pooled findings that the specific death rate related to regional recurrences was lower in the END group compared with the observation and TND groups (Fig 3A). Neither the Begg test nor the Egger test showed any publication bias ($Pr > |z| = 1.000 > .05$; $P > |t| = .604 > .05$). Sensitivity analysis verified the stability of the results (Fig 3B).

OCCULT CERVICAL LYMPH NODE METASTASIS

Occult cervical lymph node metastasis in the END group was investigated in all 6 studies. Rates of occult metastasis ranged from 20.59 to 49% (mean, 30.27%; standard deviation, 9.42%; Table 5).

TOTAL NUMBER OF RECURRENCES

Four studies reported the total number of recurrences, which could be pooled for meta-analysis. Four studies reported a smaller total number of recurrences in the END group compared with the observation and TND groups. A study by Kligerman et al[21] showed no statistical relevance. Because of minimal heterogeneity (I^2 = 0%; P = .44), a fixed-effect model was used. Meta-analysis of these 4 studies showed that the END group had a smaller total number of recurrences (RR = 0.53; 95% CI, 0.44-0.64; Fig 4A). There was no evidence of publication bias using the Begg and Egger tests ($Pr > |z| = .734 > .05$; $P > |t| = .176 > .05$). Stability of the results was acceptable (Fig 4B).

Table 3. DATA ON REGIONAL RECURRENCES, SPECIFIC DEATH RATE RELATED TO REGIONAL RECURRENCES, OCCULT CERVICAL LYMPH NODE METASTASIS, AND TOTAL NUMBER OF RECURRENCES IN INCLUDED STUDIES

Study	Outcome 1*	Outcome 2†	Outcome 3‡	Outcome 4§
Mirea et al, 2014[18]	END$^+$ 8.33% (4 of 48); END$^-$ 39.47% (15 of 38)	END$^+$ 6.25% (3 of 48); END$^-$ 31.6% (12 of 38)	27.08% (13 of 48); T1 20% (4 of 20); T2 32.14% (9 of 28)	END$^+$ 16.67% (8 of 48); END$^-$ 47.37% (18 of 38)
Fakih et al, 1989[19]	END$^+$ 30% (9 of 30); END$^-$ 57.5% (23 of 40)	END$^+$ 20% (6 of 30); END$^-$ 40% (16 of 40)	33.33% (10 of 30)	NA
Vandenbrouck et al, 1980[20]	END 7.69% (3 of 39); TND 47% (17 of 36)	END 5.13% (2 of 39); TND 13.89% (5 of 36)	49% (19 of 39)	NA
Kligerman et al, 1994[21]	END$^+$ 12% (4 of 34); END$^-$ 39% (13 of 33)	NA	20.59% (7 of 34); AT 26% (6 of 23); FM 9% (1 of 11)	END$^+$ 24% (8 of 34); END$^-$ 42% (14 of 33)
D'Cruz et al, 2015[22]	END 11.93% (29 of 243); TND 45.05% (114 of 253)	END NA; TND 23.72% (60 of 253)	29.63% (72 of 243)	END 33.3% (81 of 243); TND 57.7% (146 of 253)
Yuen et al, 2009[23]	END$^+$ 5.56% (2 of 36); END$^-$ 37.14% (13 of 35)	END$^+$ 0; END$^-$ 0	22% (8 of 36)	END$^+$ 16.67% (6 of 36); END$^-$ 45.71% (16 of 35)

Abbreviations: AT, oral tongue; END$^-$, without elective neck dissection; END$^+$, with elective neck dissection; FM, floor of mouth; NA, not available; TND, therapeutic neck dissection.

* Regional recurrences.

† Specific death rate related to regional recurrences.

‡ Occult cervical lymph node metastasis.

§ Total number of recurrences.

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Discussion

The tongue, floor of the mouth, and buccal mucosa are the most common 3 sites for oral SCC.[24] Thus, the studies included in this meta-analysis investigated oral SCC arising in these sites. The metastasis rate of the cervical lymph node in oral SCC is high, which considerably affects the survival rate.[3,25] Furthermore, occult metastasis can exist in early-stage oral SCC. The conventional or classic treatment of the primary tumor is surgery; however, radiotherapy has shown a satisfactory outcome similar to surgery in T1 and T2 cases; moreover, some studies have indicated that 5-year survival rates in early-stage (I and II) oral SCC treated with surgery or radiotherapy are similar.[26-30] Therefore, the study by Vandenbrouck et al[20] in which radiotherapy was applied to treat oral SCC was included in the systematic review. The 6 prospective studies that met the selection criteria were pooled in the meta-analysis to investigate the necessity of END for patients with oral SCC and clinically N0 neck.

Fasunla et al[31] and Ren et al[32] conducted meta-analyses of 4 and 5 RCTs, respectively, in 2011 and 2015. These meta-analyses showed the need to perform END for oral cancers with clinically N0 neck. However, the number of studies included in these meta-analyses was small. From the results of the present meta-analysis on primary outcomes, it was obvious that END substantially lowered the risk of regional recurrence (RR = 0.27) and the specific death rate (RR = 0.35). Although the 2 studies[19,20] did not report statistical relevance for the specific death rate related to regional recurrences, the synthetic result indicated statistical relevance. Previous studies reported a lower disease-specific death rate in the END group compared with the observation or TND group.[23,33] However, there was no explanation about the relation between death and regional recurrence. None of the 3 previous meta-analyses considered the outcome.[31,32,34] The present meta-analysis indicated that regional recurrence might be the main cause of disease-specific death. Hence, regional control (management of the neck) must have a positive impact on survival rate. Moreover, END is a feasible strategy to achieve satisfactory regional control.

The mean rate of occult metastasis in the END group was 30.27% based on all 6 studies, which

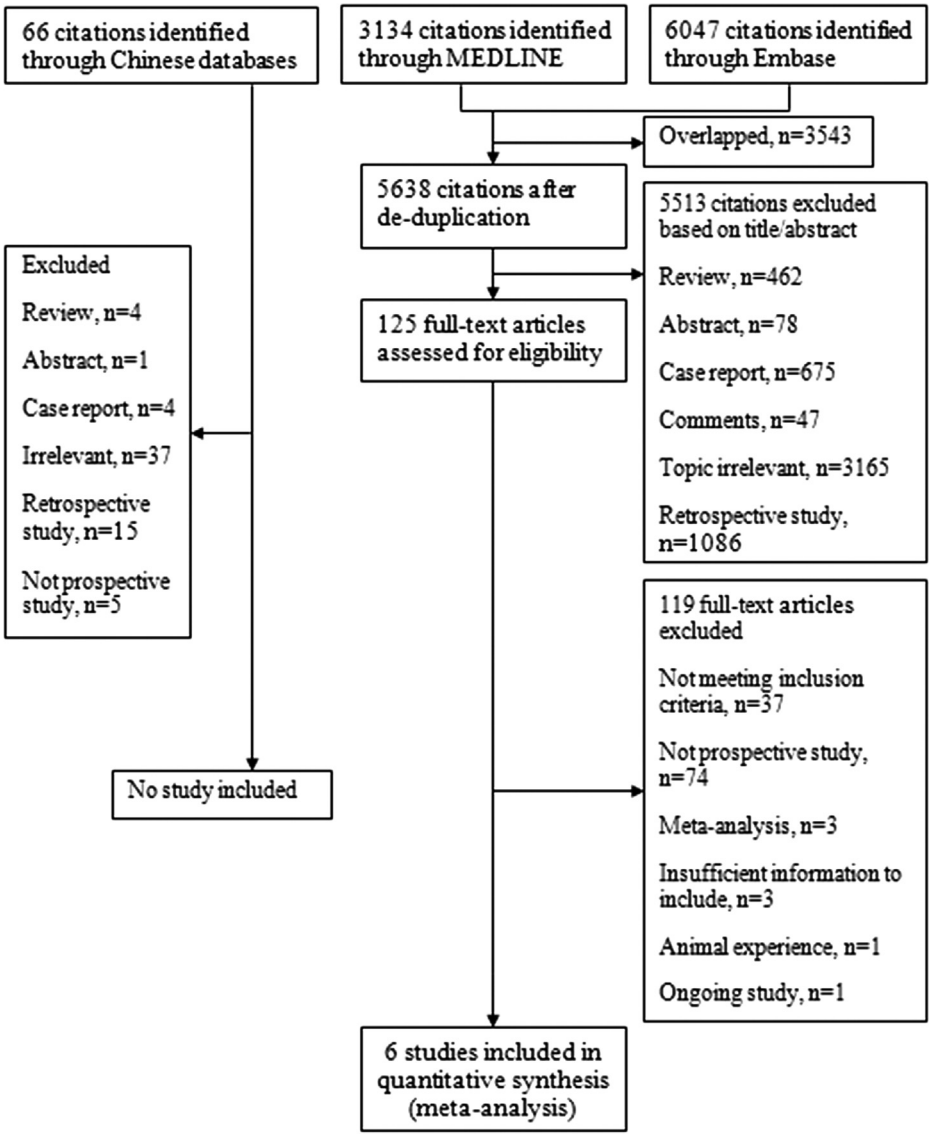

FIGURE 1. Flow diagram of selection for the study.

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coincided with other reports.[8,13-15] It is logical to conclude that one third of patients with early-stage oral SCC and clinically N0 neck are exposed to the risk of regional recurrence or metastasis. Researchers and clinicians have advocated a threshold of 15% possibility of cervical metastasis as the indication for END in SCC of the head and neck.[35] Based on these reports, END should be considered to prevent regional recurrence or metastasis. In addition, the meta-analysis showed that the total number of recurrences in the END group was considerably smaller than in the observation and TND groups (RR = 0.53; 95% CI, 0.44-0.64), which implies that END might decrease other types of recurrence apart from regional recurrence. The specific reasons require further investigation.

Although not all outcomes were pooled into the meta-analysis, some outcomes that were reported in these studies provided more information. Fakih et al[19] reported the development of cervical lymph node metastasis was statistically related to tumor depth. They found that 92% of patients (11 of 12) with a tumor depth less than 4 mm had an uninvolved node, whereas 33% of patients (3 of 9) with a tumor depth greater than 4 mm had an uninvolved node ($P < .01$). Moreover, in the observation group, 78% of patients with a tumor depth less than 4 mm and 24% of patients with a tumor depth greater than 4 mm did not develop neck node metastasis ($P < .01$). The results indicated that tumor depth influences the prognosis of oral SCC, which is in agreement with recent research.[36,37] The American Joint

Table 4. RISK OF BIAS OF INCLUDED STUDIES

Study	Aspect 1*	Aspect 2†	Aspect 3‡	Aspect 4§	Aspect 5‖	Aspect 6¶	Aspect 7#
Mirea et al, 2014[18]	LR	LR	UR	UR	LR	LR	LR
Fakih et al, 1989[19]	LR	UR	UR	UR	LR	LR	LR
Vandenbrouck et al, 1980[20]	LR	LR	UR	LR	LR	LR	LR
Kligerman et al, 1994[21]	LR	UR	UR	UR	LR	LR	LR
D'Cruz et al, 2015[22]	LR	LR	UR	LR	LR	LR	LR
Yuen et al, 2009[23]	LR	LR	LR	LR	LR	LR	LR

Abbreviations: LR, low risk; UR, unclear risk.
* Random sequence generation.
† Allocation concealment.
‡ Blinding of participants and personnel.
§ Blinding of outcome assessment.
‖ Incomplete outcome data.
¶ Selective reporting.
# Other bias.

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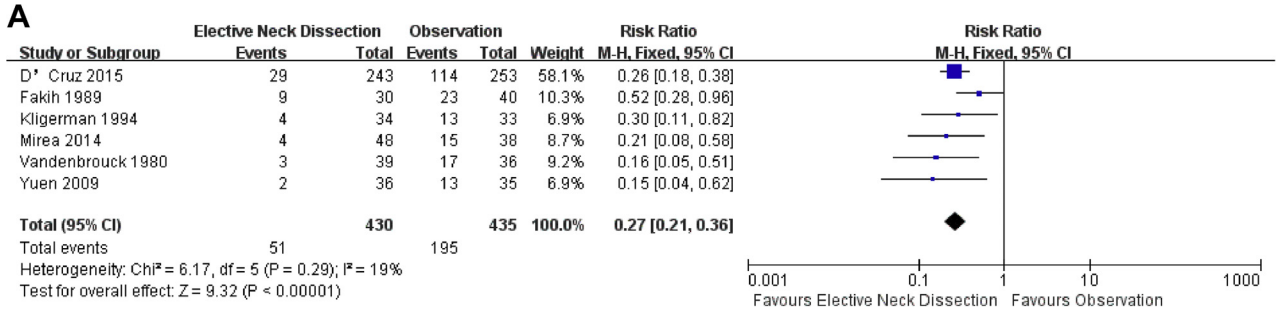

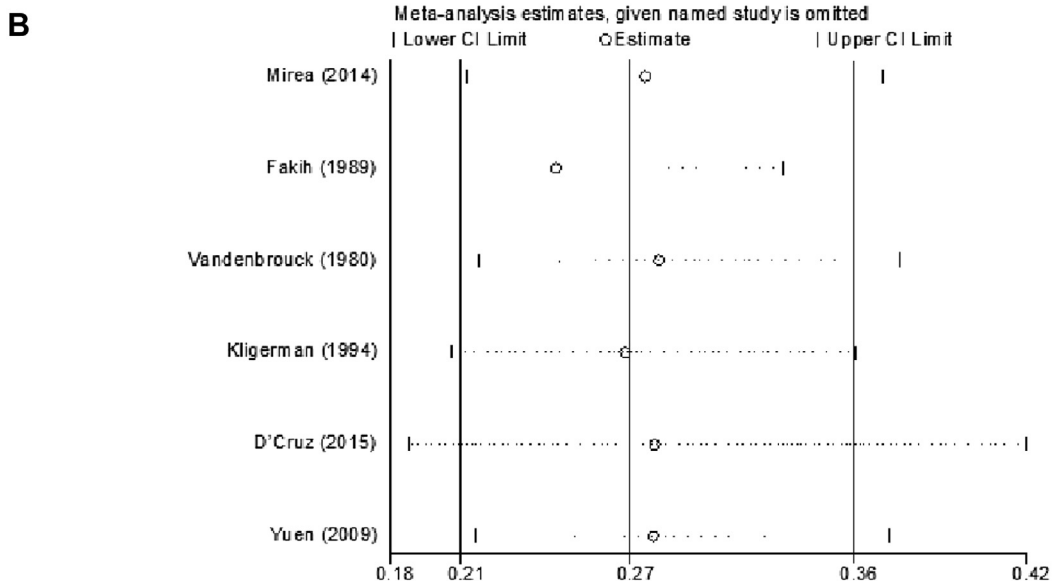

FIGURE 2. *A*, Forest plot of regional recurrences (I^2 = 19%; *P* = .29; risk ratio = 0.27; 95% CI, 0.21-0.36). *B*, Sensitivity analyses of regional recurrences. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

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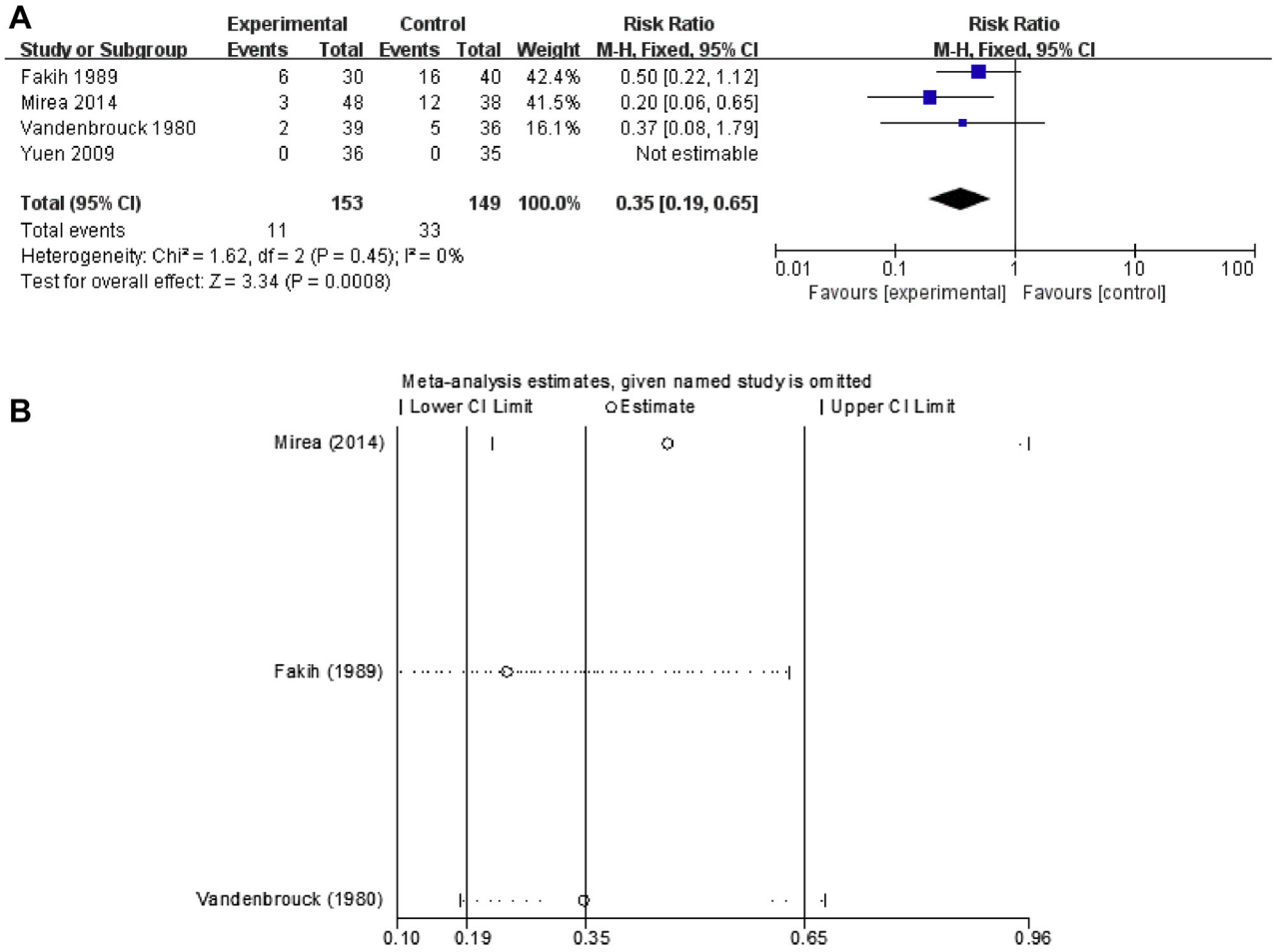

FIGURE 3. *A*, Forest plot of specific death rate related to regional recurrences (I^2 = 0%; *P* = .45; risk ratio = 0.35; 95% CI, 0.19-0.65). *B*, Sensitivity analyses of specific death rate related to regional recurrences. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

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Committee on Cancer and the International Union Against Cancer recently included depth of invasion (DOI) as a new important prognostic factor and updated the Cancer Staging Manual of the Lip and Oral Cavity (eighth edition, October 2016). In this new staging system, DOIs of 5 and 10 mm are determined as standards to decide tumor stage.

Table 5. RATES OF OCCULT CERVICAL LYMPH NODE METASTASIS IN INCLUDED STUDIES

	Rate of Occult Cervical Nodal Metastasis
Mirea et al, 2014[18]	27.08%
Fakih et al, 1989[19]	33.33%
Vandenbrouck et al, 1980[20]	49%
Kligerman et al, 1994[21]	20.59%
D'Cruz et al, 2015[22]	29.63%
Yuen et al, 2009[23]	22%
Mean	30.27%
SD	9.42

Abbreviation: SD, standard deviation.

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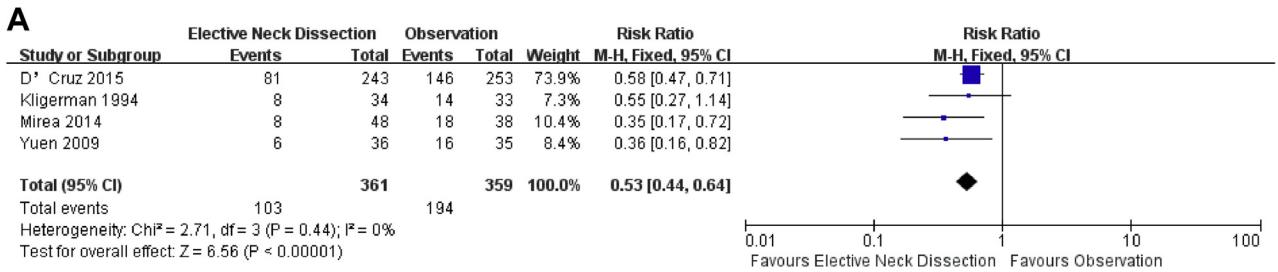
The study by Vandenbrouck et al[20] showed that the node capsular rupture rate of the END group was significantly different from that of the TND group (13 vs 30%; *P* < .05). It is generally agreed that extranodal extension (ENE) is a vital factor affecting the prognosis.[38-40] Naturally, the authors would recommend that END benefits the prognosis of early-stage oral SCC with clinically N0 neck over TND. It is worth mentioning that nodal stage is another important update of the Cancer Staging Manual of the Lip and Oral Cavity. Any lymph node with ENE is recognized as N3b.

As reported in the literature, there are varying degrees of risk for nodal involvement for tumors appearing at different sites within the oral cavity; moreover, cancers of the oral tongue and floor of the mouth are the most likely to metastasize to cervical



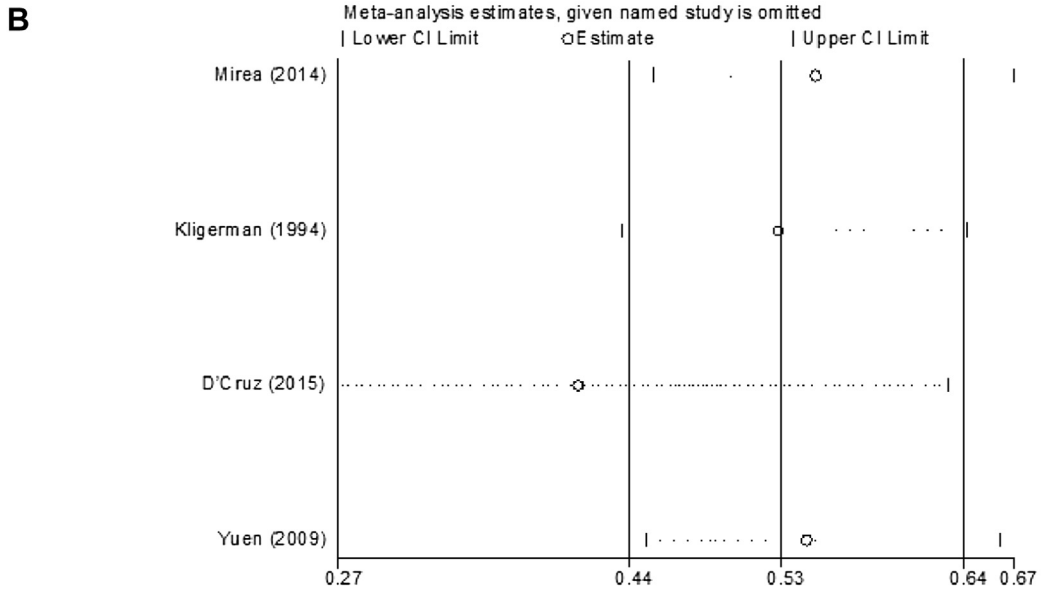


FIGURE 4. *A*, Forest plot of total number of recurrences (I^2 = 0%; *P* = .44; risk ratio = 0.53; 95% CI, 0.44-0.64). *B*, Sensitivity analyses of total number of recurrences. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

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lymph nodes.[25,41] In all the studies included in this meta-analysis, most patients had SCC of the oral tongue or floor of the mouth; thus, the present conclusions apply to these tumors with a high risk of nodal metastasis. Only 1 study, by D'Cruz et al,[22] included SCC of the buccal mucosa, which accounted for a small percentage (13.7%), whereas SCC of the oral tongue accounted for a large percentage (85.28%). Therefore, D'Cruz et al considered their conclusions were most applicable to SCC of the oral tongue. Unfortunately, subgroup analysis could not be conducted in the present meta-analysis because these parameters were not reported according to different tumor sites. Surprisingly, the results of that study, with high quality and a large sample, indicated that the tumor DOI was the main factor statistically associated with node involvement. In other words, tumor site did not make a difference in node positivity. Moreover, that study, which included SCC of the buccal mucosa, was omitted from the sensitivity analysis conducted in the present meta-analysis, and stability was confirmed. Similarly, the study by Kligerman et al,[21] which included SCC of the oral tongue and floor of the mouth, showed no relevant differences in occult nodal metastasis between the 2 oral cancers; in addition, stage and tumor thickness were regarded as relevant factors affecting prognosis. More importantly, the result of the sensitivity analysis of that study was acceptable. Hence, the conclusions drawn from the present systematic review are applicable to SCC of the oral tongue and floor of the mouth, and further studies are required to substantiate these findings.

Unfortunately, there are some limitations to this systematic review. First, the number of included studies and sample sizes were limited. Second, some included studies were antiquated. For example, the study by Vandenbrouck et al[20] was published almost 40 years ago. The diagnostic tools and level of treatment at that time undoubtedly differ from those of the present, which undervalued the comparison power. Third, not all information was reported consistently in every study. In other words, some outcomes could not be synthesized in the present meta-analysis. Fourth, the included studies investigated only oral SCC involving

the oral tongue, floor of the mouth, and buccal mucosa. There is no valid evidence that END benefits patients with oral SCC at other sites. Therefore, more multicenter studies of large samples with holistic information are required to verify the conclusions and extend them to other aspects. Moreover, there is a need to develop a much simpler, more precise, and more economical clinical examination method to detect occult metastasis of cervical lymph nodes.

In conclusion, this systematic review and meta-analysis suggests that END considerably decreases regional recurrences and the death related to it in early-stage oral SCC with clinically N0 neck, especially SCC of the oral tongue and floor of the mouth, confirming the necessity of END for these patients.

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