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Elective Neck Dissection Versus Observation in Early-Stage (cT1/T2N0) Oral Squamous Cell Carcinoma

Jin-Yong Liu, MD; Chieh-Feng Chen, MD, PhD; Chyi-Huey Bai, PhD

Objectives: Whether to perform elective neck dissection (END) or apply the observation (OBS) policy in patients with early-stage oral squamous cell carcinoma (OSCC) without clinical evidence of cervical lymph node metastasis (cT1/T2N0) remains uncertain. The two most recent meta-analyses include many studies published before the widespread availability of CT scanning in the 1990s. With the rapid advancement in imaging studies since 1990, the early clinical detection of cervical node metastasis has become more reliable without the need for END or pathological staging. Thus, we conducted a systematic review and meta-analysis of studies comparing survival outcomes between END and OBS in patients with cT1/T2N0 OSCC.

Methods: We performed a systematic search of MEDLINE, PubMed, and Scopus for retrospective and prospective studies published between January 1, 1990, and January 1, 2018, comparing clinical outcomes between END and OBS in patients with cT1/T2N0 OSCC. Information on population characteristics, study design, overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS) was extracted and estimated. Effect measures for outcomes were hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: Thirteen retrospective and two prospective randomized studies (3,158 patients) met the inclusion criteria. Compared to OBS, END failed to significantly improve OS (HR, 1.02; 95% CI, 0.95–1.09; $P = .77$; fixed-effects model), DSS (HR, 1.07; CI, 1.02–1.13; $P = .31$; fixed-effects model), and DFS (HR, 0.86; CI, 0.72–1.01; $P = .12$; random-effects model).

Conclusions: Our findings indicate that in patients with cT1T2N0 OSCC, the OBS policy can yield markedly similar OS, DSS, and DFS to those resulting from END.

Key Words: Oral cancer, elective neck dissection, observation.

Level of Evidence: 2

INTRODUCTION

Early-stage (stage I/II or cT1/T2N0) oral squamous cell carcinoma (OSCC) comprises lesions with no clinical evidence of cervical lymph node metastases (cN0) as assessed using nonsurgical examinations, such as neck palpation and imaging studies (CT, MRI, ultrasonography-guided fine needle aspiration cytology [USgFNAC], or PET). However, true pathological node-negative (pN0) disease can be confirmed only by neck dissection with lymph node biopsy. After resection of a primary oral tumor (cT1/T2N0 OSCC), physicians may perform elective neck dissection (END) to verify the presence of occult metastases (OMs) or may choose to only closely follow up with imaging studies (observation, OBS) to promptly identify any subsequent cervical lymph node metastasis; however, the most appropriate approach has remained uncertain for decades.[1,2] Even with the aid of the eighth edition of the cancer staging manual of the American Joint Committee on Cancer (AJCC), the necessity of END on patients having cT1/T2N0 OSCC with a depth of invasion (DOI) less than 4 mm remains uncertain according to National Comprehensive Cancer Network (NCCN) treatment guidelines.

OMs can only be detected by lymph node biopsy in patients undergoing END (performed during primary oral tumor resection or approximately 30 days thereafter) or present later as delayed neck recurrences on follow-up nonsurgical examinations (OBS). A neck recurrence is a cervical node metastasis that is identified after pN0 is confirmed in patients undergoing END or after a diagnosis of cN0 in patients under OBS, in the absence of local recurrence (early recurrence of primary oral cancer at a nearby site) or a second primary oral cancer.

Sentinel lymph node biopsy has high sensitivity and specificity for OM; however, because of technical difficulties, it is not widely available in many medical centers worldwide.[3]

Additional supporting information may be found in the online version of this article.

From the Graduate Institute of Clinical Medicine, College of Medicine (J.-Y.L.), Taipei Medical University, Taipei, Taiwan; Division of Plastic Surgery, Department of Surgery, Evidence-Based Medicine Center, Wan Fang Hospital (C.-F.C.), Taipei Medical University, Taipei, Taiwan; Department of Public Health, School of Medicine, College of Medicine, Cochrane Taiwan (C.-F.C.), Taipei Medical University, Taipei, Taiwan; Department of Public Health, School of Medicine, College of Medicine (C.-H.B.), Taipei Medical University, Taipei, Taiwan; School of Public Health, College of Public Health (C.-H.B.), Taipei Medical University, Taipei, Taiwan

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Send correspondence to Chyi-Huey Bai, PhD, Department of Public Health, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan. School of Public Health, College of Public Health, Taipei Medical University, Taipei, Taiwan. No. 250, Wuxing St., Xinyi Dist., Taipei City 110, Taiwan. Email: baich@tmu.edu.tw; jessiejkieh@gmail.com

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Surgical OM positivity rates of 10%–45% have been reported in cT1/T2N0 OSCC patients.[4–18] Studies have reported that once an OM evolves into clinically observable cervical lymph node metastasis, the 5-year survival rate decreases by half that in cN0 patients.[14,19] END is usually recommended when the estimated risk of OM exceeds 20%.[20] In addition to the high incidence of OM and low survival of patients with cervical metastases, studies have shown that compared with OBS, END increases the survival rate.[10,21–25] For OM, END is therapeutic and diagnostic, and the removal of metastatic lymph nodes reduces the risk of recurrence.[2,25] In addition, END allows accurate staging to establish a prognosis and to determine the need for adjuvant therapies.

Before 1990, the earliest clinical identification of cervical nodal metastasis mostly relied on neck palpation. Since 1990, with the increased availability of CT in hospitals worldwide, early clinical detection has become much more reliable.[26] In recent years, the imaging quality of ultrasonography, CT, and MRI has rapidly advanced, and PET has become more readily available. These advancements have led to more reliable preoperative nodal staging other than pathological staging.[27] Previous studies of patients with cN0 neck have shown that USgFNAC has a sensitivity of 48%–73% and a specificity approaching 100%.[28–31] Currently, the gap between a cN0 and true pN0 has decreased.

Proponents of OBS suggest that OBS can yield 5-year overall survival (OS) and disease-specific survival (DSS) rates similar to those of END if patients adhere to close follow-up with ultrasonography (i.e., once every 1–3 months during the first 3 years), CT or MRI every 6 months and undergo therapeutic (salvage) neck dissection whenever a cervical nodal metastasis is found.[32] These proponents have found that 55%–90% patients do not require END, a procedure that increases operative mortality and morbidity[18] and does not improve survival.[5,33,34] They also argue that the risks associated with END (neck pain, scarring, depression, and reduced shoulder mobility and strength) negatively impact the quality of life of patients, even in cases where functional structures are preserved during END.[35]

Several new retrospective studies have been published since the last two meta-analyses in 2016[36] and 2015.[1] Although Abu-Ghanem et al.[36] included 22 studies and Ren et al.[1] included 5 studies in their meta-analyses, several of those studies spanned decades before the advent of new, popular imaging techniques. In contrast, our investigation is limited to studies published from 1990 onward; we excluded studies conducted before 1990 because CT and MRI were not yet commonly used. Our meta-analysis has been designed to identify differences in survival outcomes between END and OBS for treating cT1/T2N0 OSCC patients based on data from studies that compared these two approaches.

MATERIALS AND METHODS

Inclusion Criteria

Studies were included if they met all the following inclusion criteria: 1) patients diagnosed with cT1/T2N0 OSCC without presurgical treatment; 2) patients underwent surgical excision of primary oral tumor with or without END; 3) clinical outcomes, including OS, DSS, disease-free survival (DFS), neck recurrence alone, and overall recurrence were reported; 4) studies were randomized controlled trials (RCTs), prospective studies, and retrospective cohort studies; and 5) reported data were relevant to the outcomes of interest.

Literature Search

MEDLINE, PubMed, and Scopus databases were used to systematically search for relevant studies published between January 1, 1990, and January 1, 2018. The keywords "oral cancer," "elective neck dissection," and "observation" were used as search terms. Among the retrieved studies, the reference lists were used as a secondary source of references. All retrieved articles were screened for clinical trials comparing END and OBS in cT1/T2N0 OSCC patients for inclusion.

Exclusion Criteria

Studies published in languages other than English and studies with insufficient prognosis data were excluded. In addition, data from patients treated with radiotherapy for primary oral cancer were excluded. Furthermore, patients who developed a second primary oral tumor were excluded in cases where such data were available.

Quality Assessment and Data Analysis

The quality and risk of bias (RoB) of all included trials were independently assessed by an independent researcher (J.Y.L.) who also performed data extraction, following the Cochrane Handbook of Systematic Review of Interventions (www.cochrane-handbook.org) guidelines (Supplementary Figs. S1 and S2 and Table S1). Any disagreement in the present study was resolved by discussion between the corresponding authors (C.H.B. and C.F.C.).

Data Extraction

Data pertaining to the study characteristics (i.e., location, year, methods, patient characteristics, sample size, and follow-up duration) were extracted (Table I). We also collected data regarding the T stage distribution (T1-T2), incidence of OM, overall recurrence, neck recurrence alone, OS, DSS, and DFS for patients subjected to END or OBS (Table II). None of the included studies or patients were duplicated, and the studies performed by Huang et al.[16,23] involved different patient populations.

Variable Definitions

The variables were defined as follows: OS, the time from the first visit to the final follow-up or death due to any cause; DFS, the time from the first visit to the development of primary oral cancer recurrence consisting of local or neck recurrence or distant metastasis; DSS, the time from the first visit to death caused by a disease attributed to primary oral cancer; and overall recurrence, combined local recurrence, cervical nodal metastases (excluding OM in the patients undergoing END), and distant metastasis of the primary oral tumor.

TABLE I.
Details of the Included Studies.

Authors and Year of Publication	Design	Country, Dates	Multicenter Study	Total Population, No.	Population Included in the Analysis, No.	END, No.	OBS, No.	Sex, Male/Female, No.	Age, Years
Sheahan et al.,[44] 2003	Retrospective	Ireland, 1990–1999	No	79	63	28	35	37/26	Mean, 61
Smith et al.,[17] 2004	Retrospective	Australia, 1988–1999	No	171	150	75	75	113/58	Median, 63
Huang et al.,[16] 2008	Retrospective	Taiwan, 1995–2002	No	380	380	324	56	325/55	Median, 48
Yuen et al.,[18] 2009	Prospective, randomized	Hong Kong, 1996–2004	Yes	72	71	36	35	43/28	Mean, OBS 58, END 56
Liu et al.,[43] 2011	Retrospective	China, 1991–2003	No	131	131	88	43	79/52	Median, 52
Flach et al.,[40] 2013	Retrospective	The Netherlands, 1990–2004	No	285	285	51	234	170/115	Median, OBS 60.8, END 56
Feng et al.,[39] 2014	Retrospective	China, 1993–2010	No	229	229	156	73	104/125	Mean, 58.1
Kelner et al.,[26] 2014	Retrospective	Brazil, 1980–2010	No	222	222	161	61	161/61	Median, 58
Huang et al.,[23] 2015	Retrospective	Taiwan, 1994–2003	Yes	173	173	151	22	167/6	Median, 50
D'Cruz et al.,[2] 2015	Prospective, randomized	India, 2004–2014	No	596	496	243	253	374/122	Mean, 48
Kim et al.,[41] 2016	Retrospective	Korea, 1990–2012	No	215	79	52	27	49/30	Mean, 56.5
Orabona et al.,[27] 2016	Retrospective	Italy, 2007–2011	No	127	127	66	61	59/68	Mean, 59.4
Liu et al.,[42] 2016	Retrospective	Canada, 2001–2007	Population-based cancer registry	447	422	100	322	256/191	Mean, 63.3
Sung et al.,[45] 2017	Retrospective	Korea, 2005–2014	No	98	98	14	84	56/42	Mean, 57
Liu et al.,[32] 2017	Retrospective	China, 2001–2011	No	232	232	181	51	123/109	Mean, END 57.5, OBS 58.6

END = elective neck dissection; OBS = observation.

Statistical Analysis

All individual outcomes were pooled using Stata (Stata Corp., College Station, Texas). The effect measures for outcomes were hazard ratios (HRs) and 95% confidence intervals (CIs). Standard errors (Se) were calculated using the formula [Log (UB) – Log(LB)]/(2 × 1.96) for studies providing HRs and upper (UB) and lower (LB) CI bounds. For studies with an available Kaplan–Meier log-rank data but no published HRs or 95% CIs, we utilized well-known methods to estimate HRs and 95% CIs,[37] that is, for studies providing a survival or recurrence rate and the number of patients treated using END and OBS, Se of HR between these groups was calculated by getting the square root of {([1 – END group rate]/[number of patients in the END group × END group rate]) + ([1 – OBS group rate]/[number of patients in the OBS group × OBS group rate])}. To obtain pooled means of survival or recurrence rates of all END or OBS groups from the included studies, Se of each single study was calculated by getting the square root of $\{(R\times[1-R])/N\}$, where R is the survival or recurrence rate of an END or OBS group from one study and N is the number of patients in that group. All study-specific estimates were combined using inverse variance-weighted averages of logarithmic HRs in both fixed- and random-effects models. Statistical heterogeneity was assessed using Chi-squared distributed Q and I^2 statistics. When significant heterogeneity was observed, with a Q value of $P < .05$ and an I^2 value of >50%, a random-effects model was used to report HRs.[38] When heterogeneity was not substantial, a fixed-effects model was used to estimate the pooled HR.

Publication Bias

The possibility of publication bias was assessed using funnel plots for any asymmetry with a 5% significance level (Figs. S3–S5).

RESULTS

Search Findings

Thirty records were retrieved from the database search, and 31 additional records were identified from reference lists of retrieved articles. Forty-six articles with irrelevant data for OSCC or survival outcomes were excluded. Figure 1 illustrates the study selection criteria and relevant reasons for exclusion. Finally, 15 studies including 3,158 patients were analyzed, comprising 1,726 patients undergoing END and 1,432 under OBS (Tables I and II).[2,16–18,23,26,27,32,39–45]

TABLE II.
Details of the T Category, Recurrence, and Survival Rates in the Included Studies.

Authors and Year of Publication	Follow-Up Time, Years	T Stage, T1/T2, No.	Occult Cervical Nodal Metastasis in the END Group, No. (%)	Overall Recurrence, END/OBS, No. (%)	Cervical Nodal Recurrence Alone, END/OBS, No. (%)	Disease-Specific Survival, END %/OBS%	Disease-Free Survival END %/OBS%	Overall Survival END %/OBS%
Sheahan et al.,[44] 2003	Mean, 4.3	NP	7 (25)	NP	6 (21.4)/5 (14.3)	3 yr: 70/88	NP	3 yr: 68/84
Smith et al.,[17] 2004	Median, 5	77/94	27 (36)	NP	4 (5.3)/15 (20)	NP	5 yr: 96/92, NS	NP
Huang et al.,[16] 2008	Median, 3.2	195/185	33 (10.1)	NP	40 (12.3)/16 (28.6)	NP	5 yr: 79/56, S	5 yr: 85.8/75, S
Yuen et al.,[18] 2009	Median, OBS 7.7, END 7.8	43/28	8 (22)	6 (16.7)/16 (45.7)	2 (5.6)/11 (31.4)	5 yr: 89/87, NS	NP	NP
Liu et al.,[43] 2011	NP	131/0	21 (23.9)	NP	13 (14.8)/10 (23.3)	NP	4 yr: 81.8/73.8, NS	4 yr: 84.1/75.9, NS
Flach et al.,[40] 2013	NP	162/123	NP	27 (52.9)/91 (38.9)	20 (39.2)/65 (27.8), NS	5 yr: 86.5/94.2, NS	NP	5 yr: 69.5/81.6, NS
Feng et al.,[39] 2014	Median, END 4.8, OBS 4.3	109/120	40 (25.6)	37 (23.7)/36 (49.3)	15 (9.6)/14 (19.2)	5 yr: 79.2/61.9, S	NP	NP
Kelner et al.,[26] 2014	Median, 5.7	84/138	33 (21)	44 (27)/18 (30)	9 (6)/5 (8)	5 yr: 85/96, NS	5 yr: 74/79, NS	5 yr: 70/77, NS
Huang et al.,[23] 2015	Median, 4.1	74/99	11 (7.3)	NP	10 (6.6)/7 (31.8), S	NP	5 yr: 82.1/59.1, S	5 yr: 79.5/81.8, NS
D'Cruz et al.,[2] 2015	Median, 3.3	219/277	NP	65 (26.7)/135 (53.4)	72 (29.6)/114 (45.1)	NP	3 yr: 69.5/45.9, S	3 yr: 80/67.5, S
Kim et al.,[41] 2016	Mean, 7.3	37/42	10 (19.2)	13 (25)/15 (55.6)	3 (5.8)/3 (11.1)	HR = 0.95, SE = 0.076, NS	NP	NP
Orabona et al.,[27] 2016	Mean, END 3.5, OBS 3.2	END 12/54, OBS 50/11	8 (12.2)	8 (12)/5 (8.2)	NP	NP	NP	NP
Liu et al.,[42] 2016	NP	NP	9 (9)	NP	10 (11)/89 (27.6)	5 yr: 80.3/80.8	NP	5 yr: 61.7/61.9
Sung et al.,[45] 2017	Mean, 2.8	70/28	4 (28.6)	6 (42.9)/17 (20.2)	3 (21.4)/8 (9.5)	NP	5 yr: 70.7/65.3, NS	5 yr: 83.3/92.4, NS
Liu et al.,[32] 2017	Median, 5.7	99/133	39 (21.5)	21 (11.6)/13 (25.5), S	9 (5)/7 (13.7), S	5 yr: 92.3/92.2, NS	NP	5 yr: 89/88.2, NS

END = elective neck dissection; NP = not provided; NS = not significant; OBS = observation; S = significant; SE = standard error.

In the analyzed studies, most of the postoperative follow-up plans for patients under OBS comprised a standard follow-up with or without ultrasonography once every 1–2 months, 2–3 months, 2–6 months, and 4–6 months for the first, second, third, and fourth–fifth years, respectively. In addition, CT or MRI was performed once every 6 months for the first year and once every 6–12 months thereafter. Whenever cervical node metastasis was identified, therapeutic (salvage) neck dissection and adjuvant therapy were performed. In the study conducted by Liu et al., neck recurrences occurred at a median of 10.8 months, and 79.8% of neck recurrences developed within 30 months among patients under OBS (322 patients).[42] In the patients undergoing END, the OM rate ranged from 7.3% to 36% (Table II). Most of the survival rates from the included studies were assessed based on a 5-year follow-up period, except for two studies with a 3-year follow-up[2,44] and one study with a 4-year follow-up.[43] In our meta-analysis, forest plots show the point estimate shifting toward the left from the line of null effect (corresponding to 1), indicating a higher survival rate for END-treated patients than for patients under OBS (Figs. 2–4).

META-ANALYSIS FOR END VERSUS OBS

Overall Survival

Our meta-analysis of 10 studies[2,16,23,26,32,40,42–45] revealed a similar OS for patients in both groups (HR, 1.02; CI, 0.95–1.09; P = .77) (Fig. 2). The between-study heterogeneity was nonsignificant (I^2 = 40.9%; P = .085); therefore, a fixed-effects model was used.

Disease-Specific Survival

Our meta-analysis of eight studies[18,26,32,39–42,44] revealed a similar DSS for patients in both groups (HR, 1.07; CI, 1.02–1.13; P = .31) (Fig. 3). The between-study heterogeneity was nonsignificant (I^2 = 38.2%; P = .125); therefore, a fixed-effects model was used.

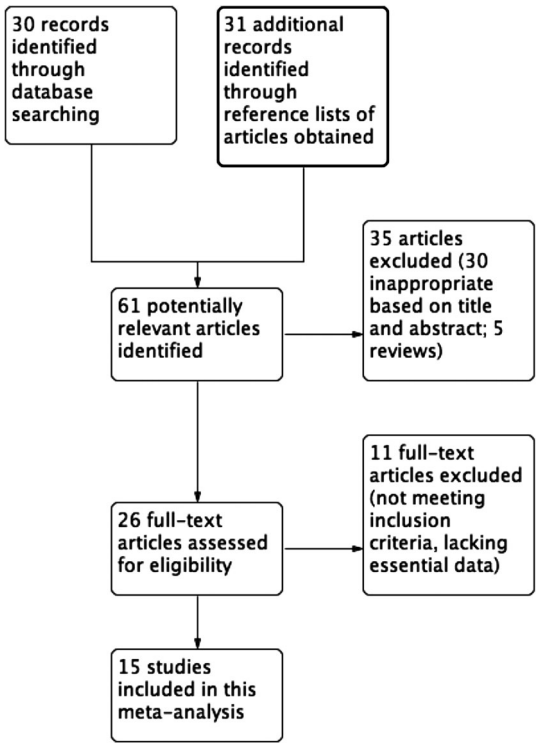

Fig. 1. Study selection for the meta-analysis.

Disease-Free Survival

Our meta-analysis of seven studies[2,16,17,23,26,43,45] revealed a nonsignificant difference between the groups in terms of DFS, but the pooled HR was shifted 14% toward the left (HR, 0.86; CI, 0.72–1.01; P = .12) (Fig. 4). The between-study heterogeneity was significant (I^2 = 72.0%; P = .002); therefore, a random-effects model was used. The significant heterogeneity was largely driven by the study by D'Cruz et al.[2]; upon exclusion of that study, the heterogeneity decreased (I^2 = 42.5%; P = .12), and a meta-analysis of the remaining six studies[16,17,23,26,43,45] revealed similar DFS in both groups (HR, 0.95; CI, 0.89–1.01; P = .47) (Fig. S6).

Overall Recurrence and Cervical Lymph Node Recurrence Alone

Our meta-analyses of 9 studies[5,18,26,27,32,39–41,45] and 14 studies[2,16–18,23,26,32,39–45] revealed lower overall recurrence and lower neck recurrence, respectively, in patients undergoing END than in patients under OBS ([HR, 1.60; CI, 1.11–2.09; P = .03; Fig. S7] and [HR, 2.23; CI, 1.64–2.83; P = .0026; Fig. S8], respectively).

META-ANALYSES FOR THE END GROUP WITH OMS VERSUS THE OBS GROUP WITH CERVICAL NODE RECURRENCE

Five-Year OS

Our meta-analysis of two studies[26,32] revealed similar OS in both groups (HR, 1.08; CI, 0.68–1.49; P = .57) (Fig. S9).

META-ANALYSES FOR THE END GROUP VERSUS THE OBS GROUP WITH T1 AND T2 PRIMARY ORAL CANCER

Five-Year OS

Our meta-analyses of two studies[32,45] revealed similar OS between END and OBS in both patients with T1 primary oral cancer (HR, 0.96; CI, 0.90–1.02; P = .48; Fig. S10) and patients with T2 primary oral cancer (HR, 0.97; CI, 0.80–1.15; P = .92; Fig. S11).

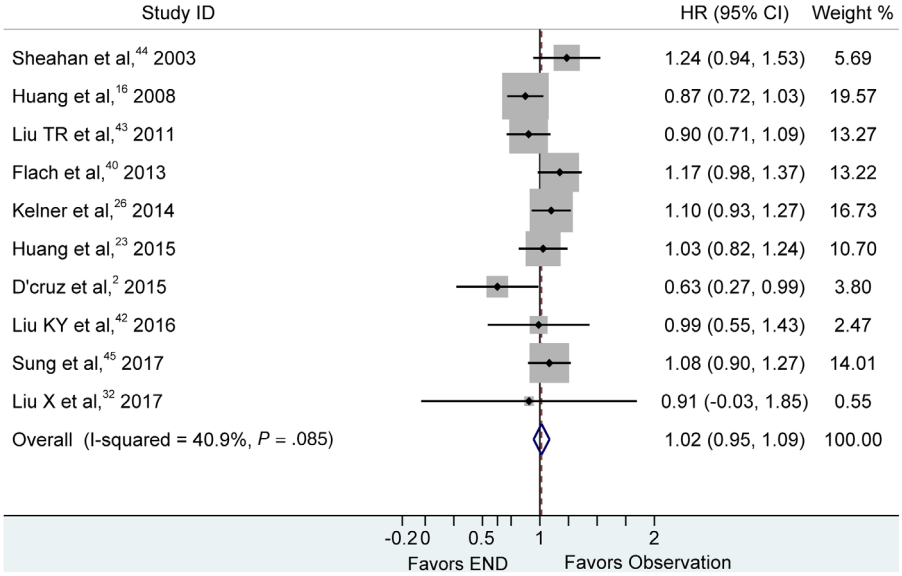

Fig. 2. Forest plot for overall survival: fixed-effects model. CI = confidence interval; END = elective neck dissection; HR = hazard ratio.

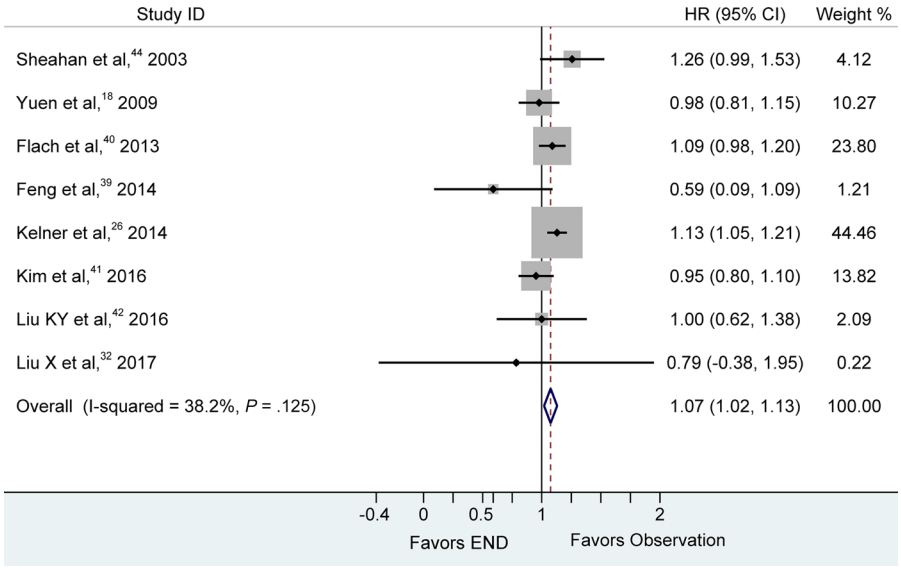

Fig. 3. Forest plot for disease-specific survival: fixed-effects model. CI = confidence interval; END = elective neck dissection; HR = hazard ratio.

Five-Year DSS

In terms of DSS, our meta-analyses of two studies[32,39] revealed a nonsignificant difference between END and OBS in both patients with T1 primary oral cancer (HR, 0.94; CI, 0.84–1.05; P = .27; Fig. S12) and patients with T2 primary oral cancer (HR, 0.85; CI, 0.41–1.28; P = .50; Fig. S13).

POOLED MEANS OF VARIABLES

The pooled means of variables in END groups and in OBS groups were 1) OS: 77% (CI, 73%–81%) and 79% (CI, 71%–86%); 2) DSS: 83% (CI, 78%–88%) and 86% (CI, 79%–93%); 3) DFS: 79% (CI, 73%–86%) and 67% (CI, 49%–85%); 4) overall recurrence: 26% (CI, 20%–32%) and 36% (CI, 26%–47%); and 5) cervical node recurrence alone: 14% (CI, 10%–18%) and 22% (CI, 16%–28%), respectively.

DISCUSSION

Eleven of the 15 included studies revealed no significant differences in survival rates. Two studies[2,16] indicated that END increased survival; one study[39] revealed higher DSS in the END group than in the OBS group but lacked data on OS and DFS; and another study[23] showed higher DFS in the END group than in the OBS group without significant differences in OS (Table II). Among

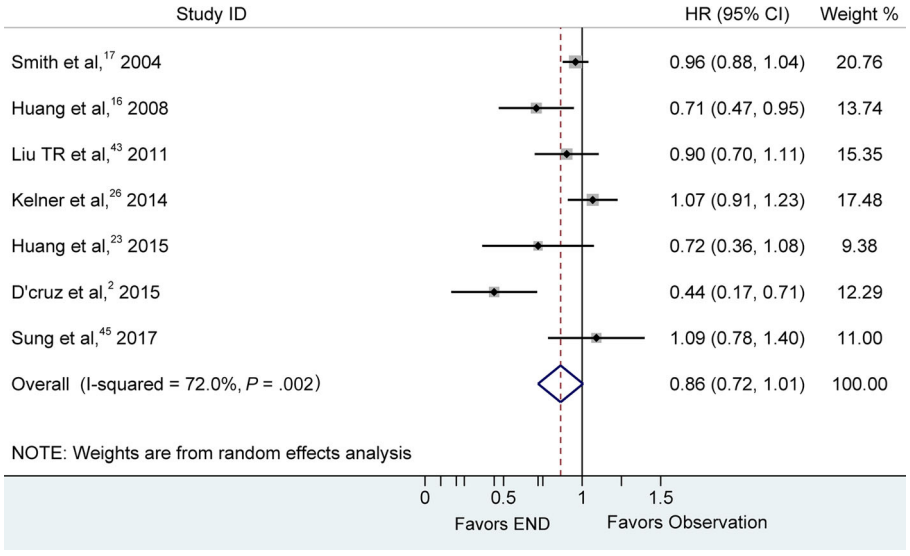

Fig. 4. Forest plot for disease-free survival: random-effects model. CI = confidence interval; END = elective neck dissection; HR = hazard ratio.

the four studies[2,16,23,39] that revealed better survival in the END group than in the OBS group, three[2,16,23] reported on DFS instead of DSS, and one[2] reported on 3-year survival instead of 5-year survival.

A large-scale prospective RCT performed by D'Cruz et al. presented encouraging results for the use of END in cT1T2N0 OSCC patients.[2] Moreover, two meta-analyses[1,36] that included the study by D'Cruz et al.[2] concluded that END improves the survival of cT1/T2N0 OSCC patients. However, in the study by D'Cruz et al.,[2] 25% of the patients had a follow-up of less than 16 months.[42] In addition, DFS is clinically less meaningful than DSS and can lead to false conclusions, that is, patients under OBS with cervical node recurrence would have had their DFS records terminated early at the first incidence of recurrence, whereas those receiving salvage neck dissections after an early identification of cervical nodal recurrence could continue to have 5-year OS and DSS similar to those of END-treated patients. There is a 7.3%–36% probability that cT1/T2N0 patients in the OBS group had OMs that eventually presented as delayed cervical node recurrences approximately 1 year from the beginning of the studies. Thus, while the DFS records for these patients likely ended early at approximately 1 year, these patients may have actually survived for more than 5 years after undergoing salvage neck dissection.

However, the OM findings in END-treated patients are not considered an endpoint for DFS. Instead, DFS of an END-treated patient ends when another new cervical node metastasis (recurrence) is identified at subsequent follow-up. Most studies agree that END reduces the chance and delays the occurrence of cervical node recurrence. Although cervical node recurrence may occur in the fourth or fifth year following END, survival rates were only followed for 3 years in the study by D'Cruz et al.[2] Therefore, the DFS of END-treated patients is likely inflated, together with the misleading, underestimated, short DFS of patients under OBS, which can lead to a false significant difference between the groups.

Additionally, the common intermittent missing of follow-up visits by some OBS-treated patients may result in distant metastasis, death, and reduced OS. However, in our meta-analysis, OS was similar between the END and OBS groups.

Missing information pertaining to examinations performed to diagnose cN0 in the study by D'Cruz et al.[2] was highlighted by de Bree[3]; moreover, the cervical node recurrence in the OBS group was as high as 45% in the study by D'Cruz et al.[2] Melchers et al.,[46] Nieuwenhuis et al.,[47] Flach et al.,[40] and our meta-analysis revealed neck recurrence rates of 18%, 21%, 28%, and 22%, respectively among cN0 patients, substantially lower than the 45% rate reported in the study by D'Cruz et al.[2] These findings suggest that there might be a less accurate diagnostic process performed for the patients in the D'Cruz et al. study[2] or a difference in population, leading to doubt regarding the generalizability of their results.[3]

The retrospective study by D'Cruz et al.[5] also showed an unusually high probability of cervical node metastasis (47%) in patients under OBS; however, neither the OS nor DFS was significantly different between the END and OBS groups.

De Bree et al.[3] concluded that OBS with strict regular USgFNAC was appropriate for cN0 OSCC patients and that END was unnecessary in most patients.

No significant difference in the OS and DSS in cT1/T2N0 OSCC patients was found between the END and OBS groups in our study (Figs. 2 and 3). The difference in DFS was not significant between the two groups (Fig. 4) when three studies with a significantly higher DFS in the END group[2,16,23] were included. When the study by D'Cruz et al.[2] was excluded, the meta-analysis of the remaining six studies revealed similar DFS in both groups and a decrease in the between-study heterogeneity (Fig. S6).

No significant difference was observed in our meta-analysis for OS in the END group with positive OM versus OS in the OBS group with cervical node recurrence (Fig. S9). In this analysis, patients with subsequent cervical node recurrence in the END group were not included in the END group with OMs, which led to an increased OS in the END group with positive OM. Interestingly, the pooled OS of patients in the OBS group with cervical node recurrence was as high as that of patients in the END group with OMs. Additionally, our meta-analysis of patients with T1 and T2 primary oral tumors in the two groups revealed no significant difference in the OS or DSS (Figs. S10–S13). However, these results must be carefully interpreted due to the small number of analyzed studies.

Previously some END proponents recommend that this procedure be performed for most stage II (T2-size) OSCC cases.[48] However, previous TNM staging system considers only tumor diameter and is not sufficient for the prognosis of early-stage OSCC tumors (some small T1 tumors behave aggressively with cervical nodal metastasis, in contrast to some large tumors that produce no metastases).[36,42] Even with recent updates to the AJCC staging system, the necessity of END on patients having cT1/T2N0 OSCC with a depth of invasion (DOI) less than 4 mm remains uncertain according to NCCN guidelines. Clinicians typically base their decision for conducting END on cT1T2N0 OSCC patients on a combination of factors, such as the tumor area, tumor size, DOI, tumor thickness, positive or negative surgical margin, and pathological features of the primary oral tumor (e.g., the presence of lymphovascular or perineural invasion). However, a consensus regarding the cutoff values of these measurements all together for conducting END is currently unavailable; therefore, further studies are warranted.

The limitations of our systematic review are the retrospective nature of most of the included studies and their relatively small sample sizes.

Our results indicate that END does not provide significant benefits of survival for managing early-stage cN0 OSCC patients. Routine END for these patients is not recommended. Our systematic review and meta-analysis indicates that in early-stage cT1/T2N0 OSCC, the survival rates of patients under close OBS are similar to those of patients undergoing END.

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