



Elective Neck Dissection Versus Therapeutic Neck Dissection in Clinically Node-Negative Early Stage Oral Cancer: A Meta-analysis of Randomized Controlled Trials

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Received: 22 September 2021 / Accepted: 24 November 2021 / Published online: 6 January 2022
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Abstract

Introduction Oral squamous cell carcinoma (OSCC) is characterized by a high risk of cervical lymph node metastasis; however, it is still not clear whether patients with early stage OSCC with clinical N0 neck should undergo elective neck dissection (END) at the time of primary tumor removal, or they should undergo a conservative approach of observation (OBS), with therapeutic neck dissection at the time of lymph nodal recurrence. We conducted a meta-analysis of randomized controlled trials (RCTs) that compared these two approaches.

Methods PubMed and Scopus databases were searched for RCTs published in English language related to END and OBS in patients with early stage OSCC with clinical N0 neck. A meta-analysis was performed using random effects model with hazard ratio (HR) as the effect size for survival parameters and odds ratio (OR) as the effect size for lymph nodal recurrence.

Results A total of 7 RCTs, comprising 1250 patients were included in the meta-analysis. Results of the meta-analyses showed that as compared to OBS approach, END could significantly improve overall survival (HR 0.67; 95% CI

0.53, 0.86) and disease-free survival (HR 0.64; 95% CI 0.46, 0.89), and significantly reduce lymph nodal recurrence (OR 0.28; 95% CI 0.12, 0.66). After correcting for heterogeneity, the disease specific survival was also found to be improved by the END approach (HR 0.53; 95% CI 0.29, 0.98).

Conclusion The results of this meta-analysis suggest that elective neck dissection at the time of resection of the primary tumor not only leads to a reduced chance of nodal recurrence, but also confers a survival benefit in patients with clinically node-negative early stage oral cancer.

Keywords Oral cancer · Tongue cancer · Buccal mucosa cancer · Elective neck dissection · Lymph node recurrence

Introduction

Oral cancer is the sixth most common cancer globally with South Asia contributing to more than one-third of the total oral cancer burden [1, 2]. Tobacco consumption, betel-quid chewing, excessive alcohol consumption, poor oral hygiene, nutrient-deficient diet, and sustained viral infections such as human papillomavirus are some of the risks associated with the occurrence of oral cancer. Oral squamous cell carcinoma (OSCC) is the most predominant form of oral cancer, and the majority of these tumors arise from the tongue, floor of mouth and buccal mucosa.

OSCC is characterized by a high risk of cervical lymph node metastasis, and frequently these metastases are occult with non-palpable neck nodes (clinical N0) [3]. Although screening of clinical N0 neck by ultrasound, CT, MRI, or positron emission tomography (PET) can help to detect some of these non-palpable nodal metastases, the recurrence rate even in radiologic N0 neck has been up to 40%

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[4]. In view of the high incidence of nodal recurrence, prophylactic neck dissection at the time of primary tumor excision has been advocated as routine management protocol of N0 neck by many surgeons. However, many surgeons on the contrary prefer watchful waiting with therapeutic neck dissection for nodal relapse. Proponents of watchful waiting approach cite the potential advantage of avoiding the neck dissection procedure in up to 70% of patients who eventually remain node-negative. In addition, neck dissection is associated with increased morbidity, complications and costs. In spite of multiple retrospective observational, prospective case–control, and randomized controlled trials (RCTs), conducted over last six decades, it is still not clear whether patients with early stage OSCC with clinical N0 neck should undergo elective neck dissection (END) at the time of primary tumor removal, or they should undergo a conservative approach of observation (OBS), with therapeutic neck dissection at the time of lymph nodal recurrence. There have been many meta-analyses also published on this subject [5–14], however, most of the previous meta-analyses had combined the results of RCTs with those of either retrospective studies or matched case–control studies, thus lowering the certainty of evidence and increasing the risk of bias.

To solve any such contentious issue, the highest quality of evidence comes from RCTs and meta-analysis of RCTs. In the present paper, we performed a meta-analysis of RCTs that compared elective neck dissection (END) at the time of primary tumor removal, with watchful observation (OBS), with therapeutic neck dissection at the time of lymph nodal recurrence in patients with clinical node-negative early stage OSCC.

Materials and Methods

Protocol and Registration

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines was consulted during the stages of design, analysis, and reporting of this meta-analysis [15]. Since, this is a meta-analysis, therefore an institutional review board or an ethics committee approval was not required. The protocol of this meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO) vide registration number CRD42020214911 and is available in full on the NIHR (National Institute for Health Research) website (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020214911).

Eligibility Criteria

The purpose of this meta-analysis was to compare the outcome of patients of clinically node-negative oral squamous cell carcinoma, who received surgical treatment of the primary tumor along with either elective neck dissection (END group) or a conservative surgical approach comprising of observation followed by therapeutic neck dissection in the event of nodal relapse (OBS group). The primary outcome of interest was overall survival, while the secondary outcomes of interest were disease specific survival, disease-free survival and frequency of lymph node recurrence.

The studies were included if they met the following inclusion criteria:

- (1) The studies were RCTs, published in English language and published between January 01, 1980 and May 01, 2021.
- (2) The included patients in the RCTs were diagnosed as clinically node-negative (cN0) oral squamous cell carcinoma (OSCC) without any prior treatment.
- (3) These patients were treated with surgical excision of the primary tumor with or without END. The patients in the END group had primary neck dissection at the time of the surgery of the primary tumor and the patients in the OBS group had surgery of the primary tumor only, while the neck was put under close observation during follow-up, and therapeutic neck dissection was performed only when neck node metastasis was detected.
- (4) The studies had reported the clinical outcomes for both these groups and the reported outcome measures included either overall survival (OS), disease specific survival (DSS), disease-free survival (DFS), or lymph nodal recurrence.

The exclusion criteria were as follows:

- (1) The primary tumor site was outside the boundaries of the oral cavity.
- (2) The study included less than 50 patients

Search Strategy and Study Selection

Comprehensive electronic searches were performed in PubMed and Scopus databases to identify relevant RCTs meeting the above inclusion and exclusion criteria. The PubMed database was searched with the following search strategy: (“cancer” OR “carcinoma” OR “neoplasm” OR “tumor” OR “squamous cell carcinoma”, OR “SCC”) AND (“neck dissection” OR “cervical lymphadenectomy” OR “observation” OR “conservative” OR “surgery” OR “resection”) AND (“lingual” OR “tongue” OR “gum”

OR “cheek” OR “buccal” OR “palatal” OR “palate” OR “floor of mouth” OR “retromolar” OR “lip” OR “labial” OR “mouth” OR “oral”)) AND (“English”[Language]). Scopus database was searched with the following search strategy: (TITLE-ABS-KEY ({elective neck dissection})) AND (carcinoma OR cancer) AND (LIMIT-TO (LANGUAGE, “English”)) AND (LIMIT-TO (EXACTKEYWORD, “Neck Dissection”)). The last search was performed on May 01, 2021. The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies and all identified articles were systematically assessed using the inclusion criteria. Other sources searched included bibliographies of previously published relevant original and review articles including meta-analyses on this topic. First, the titles and abstracts of the searched studies were screened for potential eligibility. Thereafter, the full texts of potentially eligible studies were reviewed for final inclusion. Two authors (SG and RS) independently searched, screened and selected the studies according to the search strategy, inclusion criteria and exclusion criteria.

Data Extraction

The following data were extracted from each included study: year of publication, PMID number, country of study, total number of patients in each group, their demographic data, site of cancer, tumor staging, follow-up duration, number of patients having occult LN metastasis in the END group, and clinical outcomes in terms of overall survival (OS), disease specific survival (DSS), disease-free survival (DFS), and lymph nodal recurrence. If the clinical outcome data were unavailable, these were calculated using the raw numbers provided in the studies. For discordant or unavailable data, an attempt was made to contact the corresponding authors via e-mail to provide the required data.

Risk of Bias Assessment

The methodological quality of each study was assessed using the risk-of-bias assessment tool outlined in the Cochrane Handbook for Systematic Reviews of Interventions (version 6.2) [16]. It included seven entries: the random sequence generation (for selection bias), allocation concealment (for selection bias), blinding of participants and personnel (for performance bias), blinding of outcome assessment (for detection bias), incomplete outcome data (for attrition bias), selective reporting (for reporting bias), and other bias. Since, blinding of participants and clinicians is not feasible in surgical trials, hence, performance bias was removed from the quality assessment. For each domain the risk of bias was evaluated as high, low or unclear. If any study had two or more “high-risk” entries,

it was considered to be of low quality; otherwise, it was considered to be of high quality. These results were then presented in graph form. All discrepancies were resolved by full discussions within the group of researchers.

Data Synthesis and Statistical Analysis

The meta-analysis was performed using hazard ratios (HR) with 95% confidence intervals (CIs) as the effect sizes for OS, DSS and DFS, while odds ratio (OR) as effect size for LN recurrence.

Pooling of the effect sizes were done using only a random effects model to calculate a more conservative result. $P < 0.05$ was considered to have a statistically significant difference in the outcomes between END and OBS groups. To assess the heterogeneity among studies I^2 and P values were calculated ($I^2 > 50\%$ and/or $P < 0.05$ were considered statistically significant). If there was substantial heterogeneity, the possible clinical and methodological reasons for this were explored. The meta-analysis was conducted with Review Manager software (version 5.3.5, The Nordic Cochrane Centre, Copenhagen, Denmark).

Results

Study Selection and Data Collection

Using the described search strategy 2124 studies were retrieved from the PubMed and 593 studies were retrieved from Scopus and other sources. After removing duplicates, 2130 studies were screened for potential inclusion. The titles and abstracts of these articles were screened, and 2121 studies were excluded. The full text of remaining 9 articles were examined and a further 2 articles were excluded. The study by Mirea et al. [17] was excluded because although it was prospective case-control study, it was not randomized. The study by Otsuru et al. [18] was excluded because it was propensity score matched study and not an RCT. Thus, 7 RCTs were finally included in the meta-analysis. The flow chart of the study selection is shown in Fig. 1.

Characteristics of Included Studies

The main characteristics of the included studies are summarized in Table 1. Two RCTs were from Europe, two from India, and one each from Brazil, Hong Kong, and China. A total of 1250 patients were enrolled in these studies, and of them 1019 (81%) had tongue carcinoma, 112 (9%) had carcinoma of floor of mouth, and 92 (7%) had buccal mucosa cancer. The mean / median age ranged from 48 to 62 years, and 864 (69%) patients were males.

Fig. 1 PRISMA flow diagram depicting the flow chart of study selection

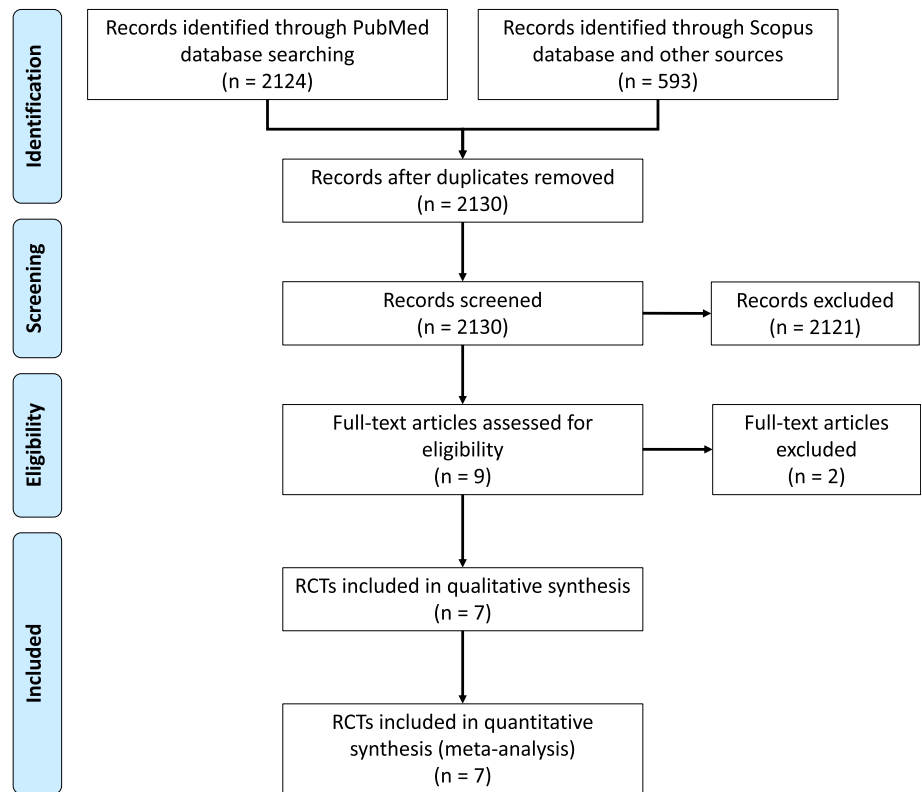


Table 1 Characteristics of the included studies

Author and year	PMID	Country	Number of patients	M:F	Age	Site (Tongue/FOM/BM/Other)	T stage (T1/T2/T3)	Occult LN metastasis in END group	Follow-up period
Vandenbrouck et al. 1980 [37]	6,992,980	France	75	67:8	57	41/34/0/0	15/48/12	19/39 (53%)	60 mo
Fakih et al. 1989 [38]	2,802,032	India	70	45:25	48	70/0/0/0	24/46/0	10/30 (33%)	20 mo
Kligerman et al. 1994 [39]	7,977,957	Brazil	67	52:15	57	41/26/0/0	31/36/0	7/34 (21%)	42 mo
Yuen et al. 2009 [40]	19,408,291	Hong Kong	71	43:28	57	71/0/0/0	43/28/0	8/36 (22%)	92 mo
D’Cruz et al. 2015 [41]	26,027,881	India	496	374:122	48	423/5/68/0	219/277/0	72/243 (30%)	39 mo
Yang et al. 2018 [19]	29,937,161	China	221	122:99	53	221/0/0/0	141/80/0	50/111 (45%)	44 mo
Hutchison et al. 2019 [42]	31,611,612	UK	250	161:89	62	152/47/24/27	159/91/0	29/126 (23%)	57 mo

The tumor stage was equally divided between stage T1 (51%) and stage T2 (48%). Only one study had 12 (1%) patients of stage T3. The frequency of occult lymph node metastasis in the END group was 32% (195/619) and ranged from 21 to 53%. The follow-up of patients ranged from 20 to 92 months.

Risk of Bias

Risk of bias assessment for each study is summarized in the Figs. 2 and 3. None of the studies had two or more of “high-risk” entries to be considered as low quality. At least 50% of studies were free of selection bias, 100% studies were free of detection bias, 70% studies were free of attrition bias, and 86% studies were free of reporting bias.

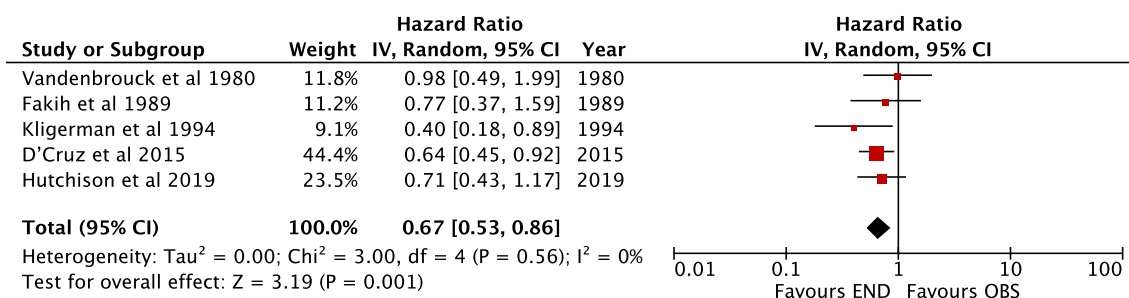


Fig. 2 Risk of bias summary: review authors’ judgments about each risk of bias item for each included study (green dot, low risk; red dot, high risk; yellow dot, unclear risk)

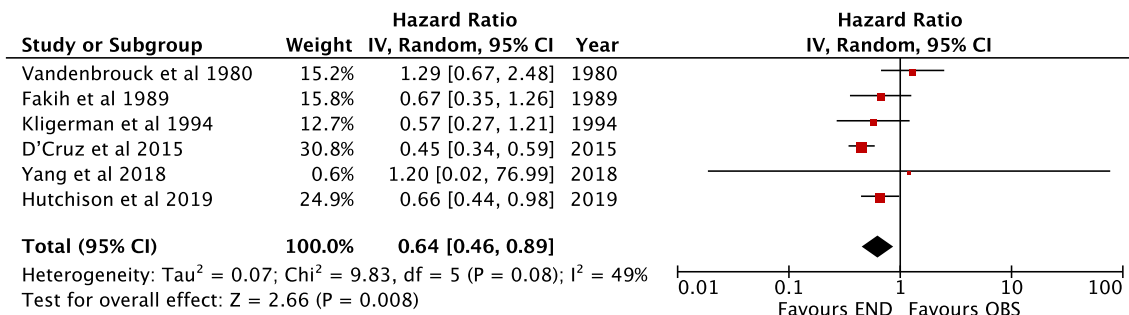


Fig. 3 Risk of bias graph: review authors’ judgments about each risk of bias item presented as percentages across all included studies

Clinical Outcomes

The clinical outcome of patients of both the groups in all the studies is given in Table 2. The HR for overall survival was provided by 5 studies, the HR for disease specific survival was provided by 5 studies, the HR for disease-free survival was provided by 6 studies, and the OR for the LN recurrence was provided by all the 7 studies.

The primary aim of this meta-analysis was to investigate the effect of END on overall survival in patients of clinically node-negative oral squamous cell carcinoma. Five of seven studies compared overall survival between the two groups (Fig. 4). The pooled HR was 0.67 (95% CI 0.53, 0.86), indicating that END led to an increase in overall survival as compared to the strategy of OBS (Fig. 4). There was no heterogeneity among the studies (P = 0.56) with an I² of 0%.

The secondary aims of this meta-analysis were disease-free survival, disease specific survival and lymph node recurrence. The pooled HR for disease-free survival was 0.64 (95% CI 0.46, 0.89), with a non-significant heterogeneity (I² 49%) (Fig. 5). The disease specific survival was found to be similar between the two groups with a pooled HR of 0.72 (95% CI 0.35, 1.49), but with significant heterogeneity (I² 68%). To look for the source of heterogeneity leave-one-out meta-analysis was performed to find out the influence of each study on the overall effect size estimate and to identify influential studies. The leave-one-

out meta-analysis revealed that the study by Yang et al. [19] was an outlier. When the meta-analysis was performed after excluding the outlier study, the pooled HR for DSS was 0.53 (95% CI 0.29, 0.98) without any significant heterogeneity (I² 34%) (Fig. 6). The pooled OR for LN recurrence was 0.28 (95% CI 0.12, 0.66), but with significant heterogeneity (I² 86%). When the meta-analysis was performed after excluding the two outlier studies the pooled OR for LN recurrence was 0.17 (95% CI 0.12, 0.24) with no heterogeneity (I² 0%) (Fig. 7).

Discussion

In this meta-analysis of 7 RCTs, comprising 1250 patients, we found that patients with early stage OSCC, who are clinically node-negative, still have 32% (range 21–53%) of occult metastasis to neck lymph nodes. As compared to the conservative OBS approach, the END approach leads to significantly improved overall survival (HR 0.67; 95% CI 0.53, 0.86) and disease-free survival (HR 0.64; 95% CI 0.46, 0.89); and also, a significantly reduce lymph nodal recurrence (OR 0.28; 95% CI 0.12, 0.66). After correcting for heterogeneity, the disease specific survival was also found to be improved by the END approach (HR 0.53; 95% CI 0.29, 0.98).

One of the most important strengths of our study is that we have included only RCTs in this meta-analysis. In

Table 2 Clinical outcomes of patients

Author and year	Group	Total	Overall deaths	HR (95% CI) Overall survival	Disease specific deaths	HR (95% CI) Disease specific survival	Free of disease	HR (95% CI) Disease-free survival	LN recurrence	OR (95% CI) LN recurrence
Vandenbrouck et al. 1980 [37]	END	39	16(41%)	0.98(0.49, 1.99)	5(13%)	0.58(0.19, 1.71)	18(46%)	1.29(0.67, 2.48)	3(8%)	0.07(0.02, 0.29)
	OBS	36	15(42%)		8(22%)		21(58%)		19(53%)	
Fakih et al. 1989 [38]	END	30	11(37%)*	0.77(0.38, 1.59)	9(30%)	0.75 0.34, 1.66)	17(57%)	0.67(0.35, 1.26)	9(30%)	0.32(0.12, 0.86)
	OBS	40	19(48%)*		16(40%)		14(35%)		23(58%)	
Kligerman et al. 1994 [39]	END	34	7(21%)	0.40(0.18, 0.89)	4(12%)	0.24(0.10, 0.58)	24(71%)	0.57(0.27, 1.21)	4(12%)	0.20(0.06, 0.72)
	OBS	33	17(52%)		16(48%)		16(49%)		13(39%)	
Yuen et al. 2009 [40]	END	36	No data	No data	4(11%)	0.97(0.24, 3.89)	No data	No data	2(6%)	0.10(0.02, 0.48)
	OBS	35	No data		4(11%)		No data		13(37%)	
D’Cruz et al. 2015 [41]	END	243	50(21%)	0.64(0.45, 0.92)	No data	No data	No data	0.45(0.34, 0.59)	29(12%)	0.16(0.10, 0.26)
	OBS	253	79(31%)		No data		No data		114(45%)	
Yang et al. 2018 [19]	END	111	No data	No data	No data	1.75(0.88, 3.49)	No data	1.2(0.02, 76.99)	30(27%)	1.77(0.93, 3.39)
	OBS	110	No data		No data		No data		19(17%)	
Hutchison et al. 2019 [42]	END	126	No data	0.71(0.43, 1.17)	No data	No data	81(64%)	0.66(0.44, 0.98)	19(15%)	0.51(0.27, 0.96)
	OBS	124	No data		No data		60(48%)		32(26%)	

* The overall deaths include patients who were lost to follow up

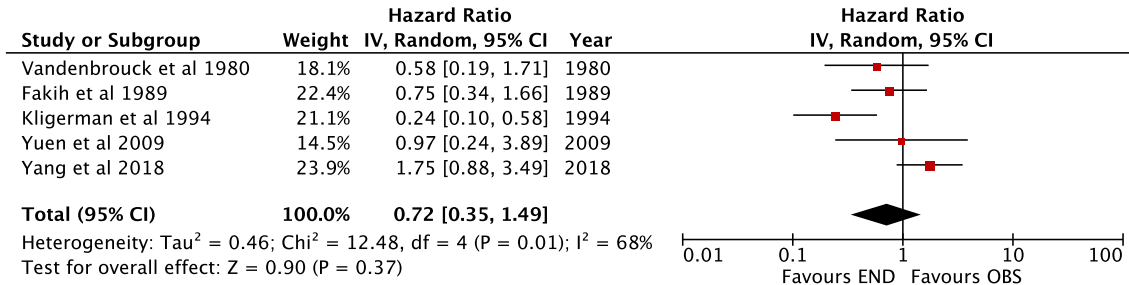


Fig. 4 Forest plot of overall survival

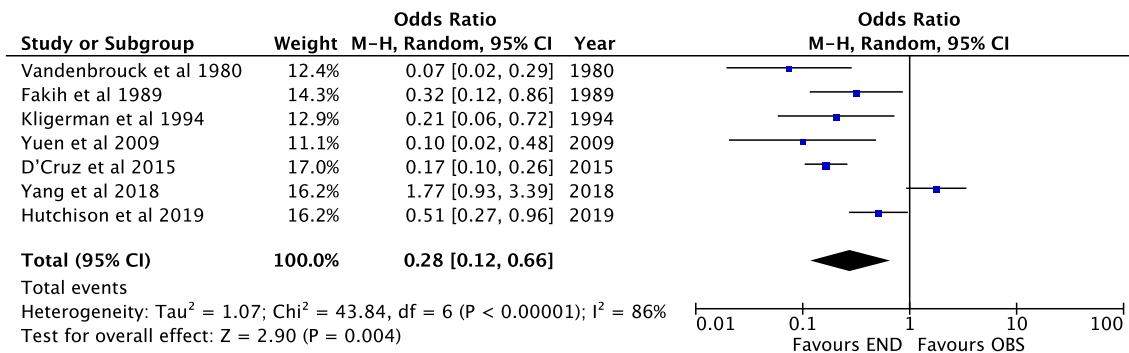


Fig. 5 Forest plot of disease-free survival

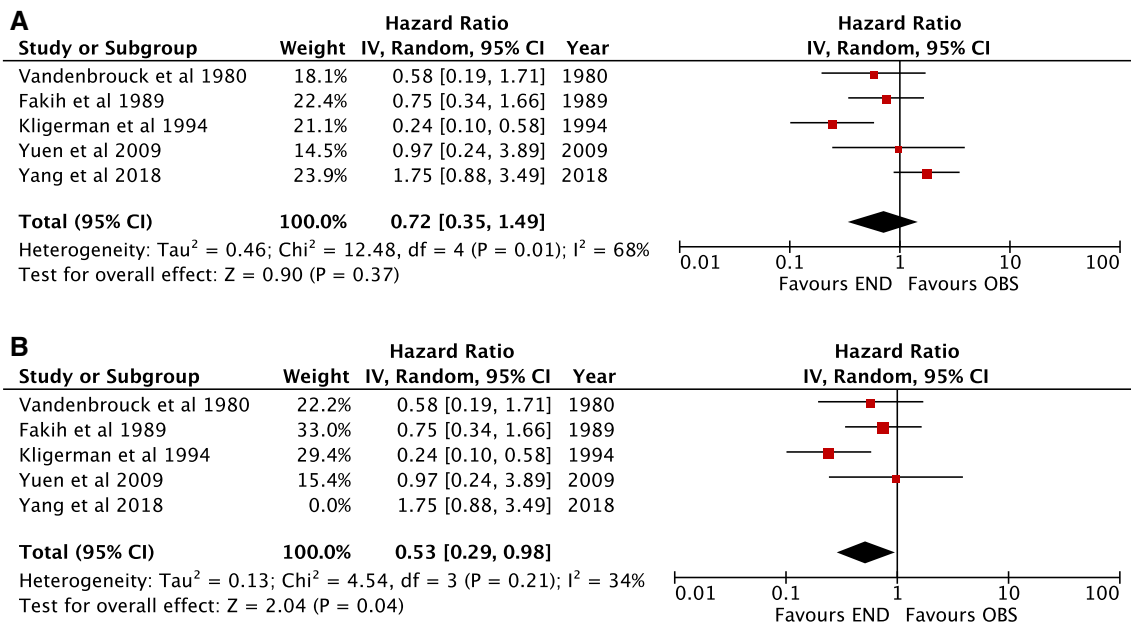


Fig. 6 (a) Forest plot of disease specific survival when all studies were included. (b) Forest plot of disease specific survival when one outlier study were excluded

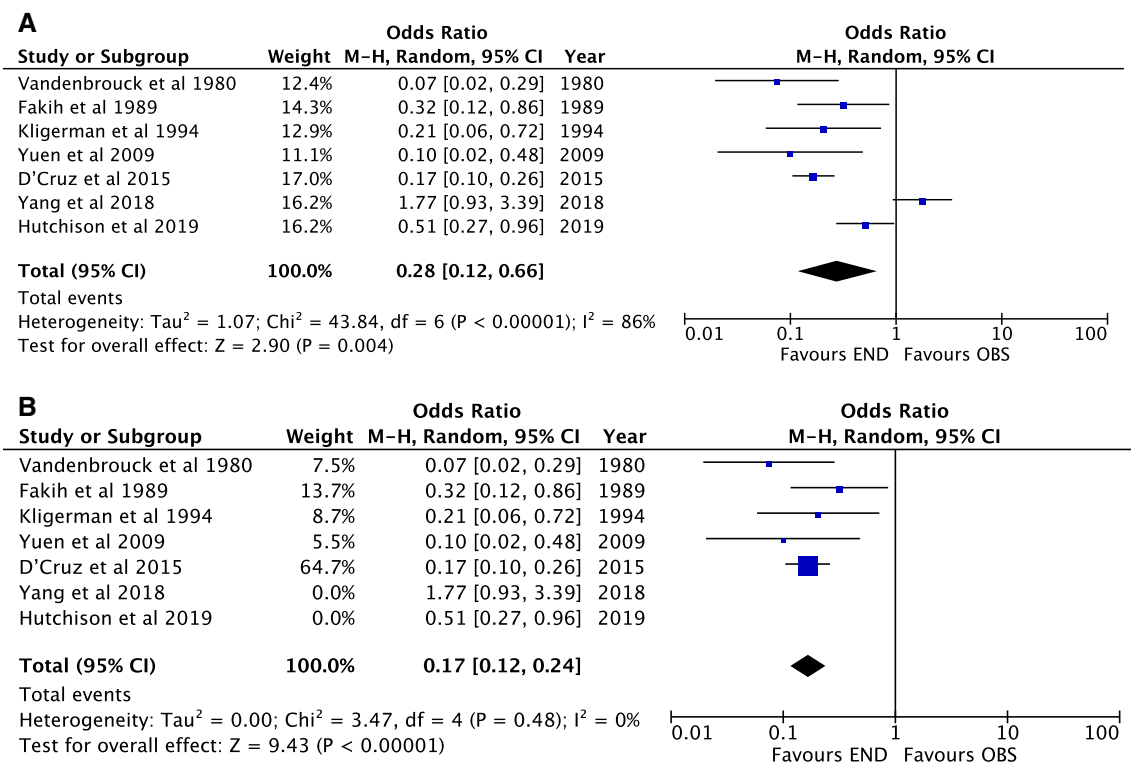


Fig. 7 (a) Forest plot of lymph node recurrence when all studies were included. (b) Forest plot of lymph node recurrence when two outlier studies were excluded

addition, we used the random effect model to pool the results and also explored the source of any significant heterogeneity using the leave-one-out meta-analysis. There have been many other meta-analyses on this subject [5–14],

however, most of the previous meta-analyses had pooled the results of RCTs with those of either retrospective studies or matched case–control studies, thus lowering the certainty of evidence and increasing the risk of bias. The

evidence generated from our meta-analysis is of high certainty, coming from input of 7 high-quality level-I trials pooled by use of rigorous statistical methods.

One of the most important adverse prognostic factors in patients with oral cancer is the presence of cervical lymph node metastasis [20, 21], as it reduces the overall survival by up to 50% [22, 23]. Patients in whom cervical lymph nodes are not palpable (clinical N0), may still harbor occult nodal metastasis [3]. Despite huge advancement in imaging technologies such as CT, MRI, and PET for preoperative noninvasive detection of cervical lymph nodal metastasis, in a significant number of patients the metastasis is missed by these imaging modalities [4, 24]. A meta-analysis comparing various modalities for the diagnosis of cervical lymph node metastasis in patient with head and neck squamous cell carcinoma with a clinically node-negative neck, found the pooled estimates for sensitivity of 47%, 57%, 48%, 63% and 56% for CT, MRI, PET, ultrasound, and ultrasound-guided fine-needle aspiration cytology, respectively [25]. Patients harboring occult cervical metastasis, in whom upfront END has not performed, present with overt lymph nodal recurrence soon after the surgery. Therefore, planning optimal management of cervical lymph nodes is a vital component of oral cancer management. Three main approaches have been advocated for clinical N0 neck management in patients with OSCC: (i) Upfront END at the time of surgery; (ii) observation (OBS), with therapeutic neck dissection if lymph nodal recurrence ensues; and more recently (iii) sentinel lymph node biopsy prior to surgery [26]. All the three approaches have their pros and cons, and despite numerous observational and interventional studies and their meta-analyses, conducted over last six decades, the best approach is still not clear. Even various society guidelines such as EHNS-ESMO-ESTRO guidelines [27], NICE guidelines [28], UK guidelines [29], NCCN guidelines [30], ASCO guidelines [31], German guidelines [32], and Indian guidelines [33], are not unanimous in their recommendations for the best approach [26]. In this direction, our meta-analysis would be a helpful addition in providing good evidence towards resolving this controversy.

We found in our meta-analysis the frequency of occult lymph node metastasis to be 32% (range 21–53%). Our results are in agreement with the meta-analysis conducted by Massey et al. who found that the rate of occult metastasis was between 21 and 49% in the 5 included RCTs, and between 7 and 39% in the 34 retrospective series [10]. Thus, it is now amply clear that one-in-three patients with clinically node-negative early stage oral cancer do harbor occult metastasis, and clinical examination of non-palpable lymph nodes cannot be relied upon when taking a decision to perform neck dissection or not. However, the question remains, is performing END in all patients the best

strategy, when two-in-three patients may not need it. In our meta-analysis, we found that the primary outcome of overall survival in patients receiving END was considerably increased in patients receiving END as compared to OBS group (pooled HR 0.67; 95% CI 0.53, 0.86). In addition, the secondary outcomes such as disease-free survival, disease specific survival, LN recurrence rates were also in favor of END approach. Thus, our meta-analysis provides strong evidence in support of elective neck dissection in patients with clinically node-negative disease.

There are a few limitations in our study. The first limitation was the presence of significant heterogeneity when the results of LN recurrence and disease specific survival were being pooled (I^2 of 86% and 68%, respectively). We were able to resolve the heterogeneity by identifying and excluding the outlier studies from our final analysis. The second limitation was that although we showed that END approach is superior to the OBS approach, but what about the third approach, i.e., the sentinel lymph node biopsy. To the best of our knowledge, there has been only one RCT that compared END with sentinel lymph node biopsy, which showed the oncologic equivalence of the sentinel LN biopsy approach to the END approach, with lower morbidity in the sentinel arm [34]. However, more studies will be needed comparing these two approaches, before any firm conclusion can be drawn.

While we and others have now shown that as compared to observation with therapeutic neck dissection approach, the elective neck dissection should be the preferred approach in the management of clinically node-negative early oral cancer, even this aggressive approach may still not guarantee against future recurrences. A meta-analysis of 21 studies that studied regional recurrence in the pathologically node-negative neck dissection (pN0) neck following END approach, still observed a recurrence rate of 7.5% over a median follow-up of about 3 years [35]. Thus, although the END approach should be preferred, however, this is still not the Holy Grail of best approach and other strategies should also be explored. Bree et al. have proposed to develop decision models that can serve to optimize choices depending on relevant variables such as individualized risk of lymph node recurrence, patient and institutional preference, and other factors, rather than proposing any one approach for all patients [36].

In conclusion, the results of our meta-analysis of seven randomized controlled trials suggest that elective neck dissection at the time of resection of the primary tumor not only leads to a reduced chance of nodal recurrence, but also confers a survival benefit as compared to the conservative approach of watchful waiting and therapeutic neck dissection at the time of lymph nodal recurrence in patients with clinically node-negative early stage oral cancer.

Acknowledgements Authors declare that there is no conflict of interest.

Author contributions All the authors made substantial contributions to the conception and design of the work, analysis, and interpretation of data. SG drafted the manuscript. AK, SM and RS revised it critically for important intellectual content. All the authors approved the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding This study did not receive any funding.

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