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HEAD AND NECK

Elective neck dissection in T1/T2 oral squamous cell carcinoma with N0 neck: essential or not? A systematic review and meta-analysis

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Abstract

Introduction Oral squamous cell carcinoma (SCC) is characterized by a high risk of cervical lymph node metastasis with a high incidence of occult metastasis. A strong debate is still present regarding the best treatment for early oral cavity cancer with N0 neck.

Objective The aim of the present study was to compare between the results of elective neck dissection (END) and watchful waiting (observation or therapeutic neck dissection) in patients with early-stage (T1/T2) oral squamous cell carcinoma with N0 neck.

Data sources Medline database (https://www.pubmed.com), Google Scholar and Scopus.

Patients and methods A systematic review and meta-analysis for the evaluation of regional recurrence rate and 5-year survival rate after elective neck dissection (END) or watchful waiting in early oral cancers were conducted. This study included published English medical articles (which met our predetermined inclusion criteria) in the last 30 years, concerning early oral SCC with N0 neck. 24 articles were included (4 randomized studies and 20 observational "retrospective" studies) with a total number of 2190 of patients who underwent END and 1619 who underwent watchful waiting. Regarding the 5-year survival rate, (10) studies were included with a total number of 1211 patients who underwent END and 948 who underwent watchful waiting.

Results Regarding the regional recurrence rate, (END) was associated with significantly lower risk of recurrence when compared with observation. Regarding the 5-year survival rate, END was associated with a better survival rate than the observational group.

Conclusions Elective neck dissection is better than watchful waiting in early (T1/T2) stage oral cavity squamous cell carcinoma with N0 neck, regarding regional recurrence and 5-year survival rate.

Keywords Early oral SCC · Squamous cell carcinoma · Cervical neck dissection · T1/T2 oral cancers · N0 neck and oral tongue

Introduction

The oral cavity includes the buccal mucosa, anterior two-thirds of the oral tongue, retromolar trigone, lips, floor of the mouth, hard palate and alveolar ridge. Squamous cell carcinoma (SCC) is responsible for more than 90% of the head and neck tumors arising from the oral cavity and oropharynx [1]. Lymph node metastases is the most significant prognostic factor for recurrence and survival rate, reducing the survival rate by 50% [2].

Elective (prophylactic) neck treatment of the cervical nodes is performed to avoid the spread of an occult metastasis when the risk of occult metastases exceeds 15–20%

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[3]. Apart from carcinoma of the lips and hard palate, which have a lower incidence of cervical nodal metastasis at diagnosis, oral squamous cell carcinoma (OSCC) is characterized by a high incidence of early metastases to cervical lymph nodes (with levels 1–3 being the first-echelon lymph nodes), particularly tumors arising from oral tongue and floor of mouth [4, 5].

More than 30% of the patients with oral cavity cancer and clinically N0 neck have occult cervical nodal metastases at diagnosis. The incidence depends on the primary tumor site, depth of the tumor and its histopathologic type [6].

A strong debate about neck treatment for early-stage squamous cell carcinoma of the oral cavity (stages I and II) with clinically negative necks exist. Both elective neck dissection and "watchful-waiting" policy have their proponents. The debate arises from the fact that routine prophylactic neck treatment will add unnecessary cost and morbidity, while there is no preoperative investigation (up till now) to be 100% sure that nodal micro-metastasis does not exist, which if neglected will lead to poor regional control and decrease survival rate [7].

Aim of the study

The aim of this systematic review and meta-analysis study was to assess the need for elective neck dissection (END) in early-stage (T1/T2) OSCC with N0 neck by comparing the results of regional recurrence and 5-year survival rate in patients who underwent END versus watchful-waiting policy (therapeutic neck dissection) through analysis of prospective "randomized controlled trials" and retrospective "observational" studies.

Materials and methods

This study was done in the following steps.

- Determination of the target subject.
  Patients diagnosed with early (T1/T2) oral SCC with N0 neck.
- Identification and location of articles.
  This study was limited to published medical articles in English language in the last 30 years (1989–2018) with stage I (T1N0M0) or stage II (T2N0M0) oral squamous cell carcinoma (OSCC) in six areas (oral tongue, buccal mucosa, hard palate, alveolar margins, floor of the mouth and retromolar trigone), excluding cancer of the lips. This study was conducted through searching the Medline database (https://www.pubmed.com), Google Scholar and Scopus, using a combination of the following keywords: early oral SCC; squamous cell carcinoma; cervical neck dissection; T1/T2 oral cancers; N0 neck and oral tongue.

Included articles

- Published in English language.
- Published in the last 30 years.
- Patients with oral SCC in six areas of the oral cavity (oral tongue, buccal mucosa, hard palate, alveolar margins, floor of mouth and retromolar trigone), excluding cancer of the lips.
- Patients with pathologically proven SCC of the oral cavity.
- Patients with N0 neck clinically and radiologically.
- Patients with oral squamous cell carcinoma who received surgical treatment only.
- Patients did not receive previous neck radiotherapy

Study design Randomized control trials (prospective) and observational "retrospective" studies.

Type of intervention Elective neck dissection (END) versus watchful waiting (observation or therapeutic neck dissection).

Articles which miss one or more of the above-mentioned inclusion criteria, such as articles not in English, non-SCC oral cavity tumours, clinically positive neck nodes at diagnosis, neck treatment with radiotherapy and late stage oral cavity cancer were excluded.

Medline search was done with blinding of the author's name and journal's name. Over 1200 articles were identified. After removal of duplicates (460), the identified articles decreased to 740 articles. After exclusion of non-relevant articles (695), 45 articles were found to be relevant. Applying the inclusion criteria, 24 articles were found to match them and selected for further steps of data analysis.

- Data extraction.
  Information was gathered from each individual study (Table 1), extracting data about:

  - The site of the tumor.
  - Total number of patients in each study and number of cases who underwent elective neck dissection (END group) or watchful waiting.
  - Type of END.
  - The results of regional control and 5-year survival rate in both groups (END group versus observational group).

Data were independently extracted by two reviewers and cross-checked.

Table 1 Included articles

Articles	Site of the tumor	Total number of patients in the study (*n*)	END group	Watchful-waiting group	END group (eventful)	END (uneventful)	Observed group (eventful)	Observed group (uneventful)	5-year survival rate in END group (%)	5-year survival rate in observed group (%)	Type of END	Study type
Fakih et al. [2]	Oral tongue	70	30	40	10	20	23	17			RND	Prospective randomized
Franceschi et al. [38]	Oral tongue	211	63	148	26	37	39	109			RND, MRND, SOHND	Retrospective
Kligerman et al. [22]	Oral tongue, floor of mouth	67	34	33	8	26	14	19			SOHND	Prospective randomized
Beenken et al. [39]	Oral tongue	153	15	138	6	9	31	107	90	54	SOHND	Retrospective
Yii et al. [40]	Oral tongue	77	27	50	7	20	20	30	75	65	SOHND, MRND	Retrospective
Dias et al. [30]	Oral tongue, floor of mouth	49	24	25	1	23	6	19			SOHND, MRND	Retrospective
Goto et al. [31]	Oral tongue	90	33	57	8	25	15	42			Not mentioned	Retrospective
Keski-Säntti et al. [33]	Oral tongue	78	44	34	8	36	15	19			Not mentioned	Retrospective
Capote et al. [27]	Oral tongue, floor of mouth, gingiva, retromolar trigone	154	87	67	7	80	18	49	92	77	Not mentioned	Retrospective
Huang et al. [32]	Oral tongue	380	324	56	40	284	16	40			SOHND, MRND	Retrospective
D'Cruz et al. [41]	Oral tongue	359	159	200	32	127	94	106	74%	68%	SOHND, MRND	Retrospective
Yuen et al. [42]	Oral tongue	71	36	35	2	34	13	22	89	87	SOHND	Prospective randomized
Liu et al. [34]	Oral tongue	131	88	43	21	67	10	33			SOHND, SND (I–IV)	Retrospective
Lin et al. [43]	Oral tongue	81	29	52	7	22	20	32			SOHND, MRND, SND (I–IV)	Retrospective
Pugazhendi et al. [44]	Oral tongue	21	11	10	0	11	2	8			Not mentioned	Retrospective

Table 1 (continued)

Articles	Site of the tumor	Total number of patients in the study (*n*)	END group	Watchful-waiting group	END group (eventful)	END (uneventful)	Observed group (eventful)	Observed group (uneventful)	5-year survival rate in END group (%)	5-year survival rate in observed group (%)	Type of END	Study type
Tai et al. [45]	Oral tongue, floor of mouth, buccal mucosa, retromolar trigone and hard palate	264	170	94	16	154	21	73			SOHND	Retrospective
Beltramini et al. [46]	Maxillary gingiva, alveolus and hard palate	20	5	15	0	5	2	13			MRND, SND (I–IV)	Retrospective
Feng et al. [47]	Oral tongue	222	151	71	15	136	14	57	94	87	SOHND, MRND, RND	Retrospective
Kelner et al. [48]	Oral tongue, floor of mouth	222	161	61	33	128	10	51	58	69	SOHND, MRND, RND, SND (I–IV)	Retrospective
Huang et al. [49]	Buccal mucosa	173	151	22	10	141	7	15	80	81	SOHND, MRND	Retrospective
Peng et al. [4]	Oral tongue	123	88	35	10	78	4	31			Not mentioned	Retrospective
Zhang et al. [35]	Oral tongue	65	36	29	8	28	6	23			SOHND	Retrospective
D'Cruz et al. [28]	Oral tongue, buccal mucosa, floor of mouth	496	243	253	25	218	108	145	80	69	SOHND, MRND	Prospective randomized
Liu et al. [50]	Oral tongue, buccal mucosa, floor of mouth, mandibular gingiva	232	181	51	21	160	13	38	89	76	Not mentioned	Retrospective

END elective neck dissection, *RND* radical neck dissection, *MRND* modified radical neck dissection, *SOHND* supraomohyoid neck dissection, *SND* selective neck dissection

Statistical methods

Statistical analysis was done using an Openmeta software (https://openmeta.metamorphsoftware.com/).

Testing for heterogeneity

Studies included in the meta-analysis were tested for heterogeneity of the estimates using the following tests:

- Cochran Q Chi square test: a statistically significant test (p value < 0.1) denoted heterogeneity among the studies.
- I square (I^2) index which reflects the inconsistency in the effect size measured in the meta-analysis. It may be interpreted—although not universally accepted—as follows.

I^2 = 0–25%: unimportant heterogeneity.
I^2 = 25–50%: moderate heterogeneity.
I^2 = 50–75%: substantial heterogeneity.
I^2 = 75–100%: considerable heterogeneity.

Examination of publication bias

Publication bias was assessed by examination of the funnel plots of the effect size measures and the Begg–Mazumdar rank correlation and Egger regression tests. The funnel plot is a plot of the estimated effect size on the horizontal axis versus a measure of study size (standard error for the effect size) on the vertical axis. Publication bias results in asymmetry of the funnel plot. If publication bias is present, smaller studies will show larger effects. The funnel plot may not always be a reliable tool, especially when the number of studies included in the analysis is small.

Pooling of estimates

Comparison of binary outcomes was done by estimation of the risk ratios (RR) with their 95% confidence interval (CI) and risk difference or risk reduction with their 95% CI. The incidence of the bad outcome was measured in both intervention and control groups, where incidence = number of events (regional recurrence) in a group divided by the total number of patients in this study.

Estimates from included studies were pooled using the DerSimonian and Laird random effects method (REM) and the Mantel–Haenszel fixed effects method (FEM). In the presence of significant heterogeneity, the REM was considered. Otherwise, the FEM was considered. p values < 0.05 are considered statistically significant.

Results

Regional recurrence rate

Randomized "prospective" clinical studies (N = 4)

Four studies were included, with a total number of 343 in the END group and 361 in the control group.

- *Risk ratio* (Table 2, Fig. 1) There was a significant heterogeneity among the included studies (Cochran Q = 9.7521, df = 3, p = 0.0208, I^2 = 69.24%). Under the random effects model (REM), END was associated with a risk of regional recurrence = 36.1% of that in the control group (RR = 0.361, 95% CI 0.197–0.660, p = 0.001). There was no evidence of publication bias by examining the Funnel plot, Egger: bias = 0.591587, p = 0.8522.
- *Risk difference* (Table 2) There was no significant heterogeneity among the included studies (Cochran Q = 1.6567, df = 3, p = 0.6466, I^2 = 0.0%). Under the fixed-effect model (FEM), END was associated with

Table 2 Meta-analysis for the randomized control articles (risk ratio and risk difference of regional recurrence)

Study	Intervention	Controls	Relative risk Z test = 3.309, p = 0.001			Risk difference Z = 9.565, p < 0.001		
			Relative risk	95% CI	Weight (%) random	Risk difference	95% CI	Weight (%) random
Fakih et al. [2]	10/30	23/40	0.580	0.327–1.027	29.00	−0.242	−0.470 to −0.0138	7.27
Kligerman et al. [22]	8/34	14/33	0.555	0.269–1.145	25.05	−0.189	−0.410 to 0.0319	7.74
Yuen et al. [42]	2/36	13/35	0.150	0.0364–0.615	12.44	−0.316	−0.493 to −0.139	12.08
D'Cruz et al. [28]	25/243	108/253	0.241	0.162–0.359	33.51	−0.324	−0.396 to −0.252	72.92
Total (random effects in risk ratio and fixed effects in risk difference)	45/343	158/361	0.361	0.197–0.660	100.00	−0.302	−0.364 to −0.240	100.00

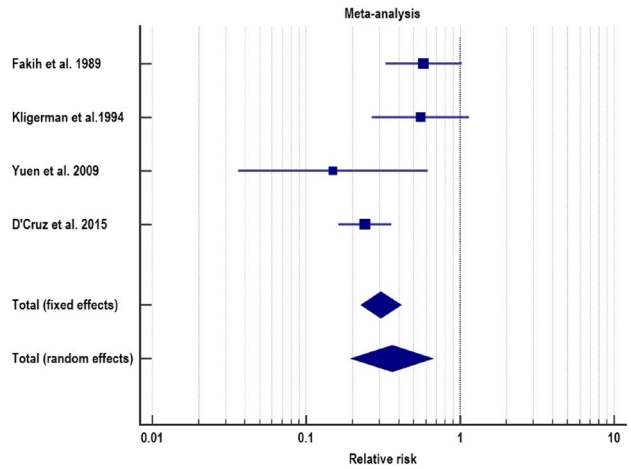

Fig. 1 Forest plot for risk ratio in the four clinical trial studies

a risk of regional recurrence that was 30.2% less than the same risk in the control group (RD = 0.302, 95% CI 0.240–0.364, $p < 0.001$). There was no evidence of publication bias on examining the funnel plot, Egger: bias = 1.100238, $p = 0.1773$.

Observational "retrospective" studies ($N = 20$)

Twenty studies were included in the analysis with a total number of 1847 of cases in the END group and 1258 cases in the watchful-waiting group.

- *Risk ratio* (Table 3, Fig. 2) There was a significant heterogeneity among the included studies (Cochran $Q = 61.1626$, $df = 19$, $p < 0.001$, $I^2 = 68.94\%$). Under the random effects model (REM), END was associated with a risk of recurrence = 63.1% of the watchful-waiting group (RR = 0.631, 95% CI 0.472–0.842, $p = 0.002$). There was no evidence of publication bias by examining the funnel plot, Egger: bias = −0.544464, $p = 0.5968$.
- *Risk difference* (Table 3) There was a significant heterogeneity among the included studies (Cochran $Q = 51.385$, $df = 19$, $p = 0.001$, $I^2 = 63.02\%$). Under the random-effect model (REM), END was associated with a risk of recurrence that was 9.87% less than the same risk in the watchful-waiting group (RD = 0.0987, 95% CI 0.0439–0.154, $p < 0.001$). There was no evidence of publication bias on examining the funnel plot, Egger: bias = 0.731823, $p = 0.5301$.

Table 3 Meta-analysis for the retrospective articles (risk ratio and risk difference of regional recurrence)

Study	Intervention	Controls	Relative risk $Z = 3.125$, $p = 0.002$			Risk difference $Z = 3.530$, $p < 0.001$		
			Relative risk	95% CI	Weight (%) random	Risk difference	95% CI	Weight (%) random
Franceschi et al. [38]	26/63	39/148	1.566	1.051–2.334	7.20	0.149	0.00841–0.290	5.48
Beenken et al. [39]	6/15	31/138	1.781	0.890–3.561	5.64	0.175	−0.0822 to 0.433	2.97
Yii et al. [40]	7/27	20/50	0.648	0.315–1.335	5.49	−0.141	−0.355 to 0.0732	3.72
Dias et al. [30]	1/24	6/25	0.174	0.0225–1.337	1.62	−0.198	−0.384 to −0.0128	4.33
Goto et al. [31]	8/33	15/57	0.921	0.438–1.937	5.38	−0.0207	−0.206 to 0.165	4.33
Keski-Säntti et al. [33]	8/44	15/34	0.443	0.221–0.891	5.62	−0.246	−0.448 to −0.0430	3.95
Capote et al. [27]	7/87	18/67	0.299	0.133–0.675	5.03	−0.188	−0.309 to −0.0676	6.07
Huang et al. [32]	40/324	16/56	0.432	0.261–0.716	6.65	−0.162	−0.286 to −0.0386	5.98
D'Cruz et al. [41]	32/159	94/200	0.428	0.304–0.603	7.47	−0.269	−0.362 to −0.176	6.88
Liu et al. [34]	21/88	10/43	1.026	0.531–1.983	5.82	0.00608	−0.148 to 0.161	5.10
Lin et al. [43]	7/29	20/52	0.628	0.302–1.304	5.44	−0.143	−0.348 to 0.0611	3.91
Pugazhendi et al. [44]	0/11	2/10	0.183	0.00985–3.413	0.87	−0.200	−0.448 to 0.0479	3.11
Tai et al. [45]	16/170	21/94	0.421	0.231–0.767	6.14	−0.129	−0.224 to −0.0343	6.83
Beltramini et al. [46]	0/5	2/15	0.533	0.0297–9.575	0.89	−0.133	−0.305 to 0.0387	4.65
Feng et al. [47]	15/151	14/71	0.504	0.257–0.986	5.75	−0.0978	−0.202 to 0.00628	6.55
Kelner et al. [48]	33/161	10/61	1.250	0.657–2.379	5.90	0.0410	−0.0709 to 0.153	6.32
Huang et al. [49]	10/151	7/22	0.208	0.0884–0.490	4.82	−0.252	−0.451 to −0.0533	4.04
Peng et al. [4]	10/88	4/35	0.994	0.334–2.962	3.81	−0.000649	−0.125 to 0.124	5.95
Zhang et al. [35]	8/36	6/29	1.074	0.420–2.746	4.44	0.0153	−0.185 to 0.216	4.00
Liu et al. [50]	21/181	13/51	0.455	0.245–0.844	6.04	−0.139	−0.267 to −0.0105	5.84
Total (random effects)	277/1847	363/1258	0.631	0.472–0.842	100.00	−0.0987	−0.154 to −0.0439	100.00

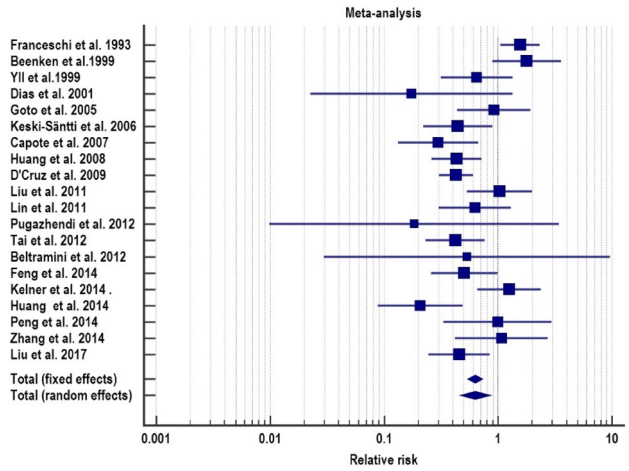

Fig. 2 Forest plot of risk ratio of regional recurrence in the observational studies

The pooled estimates of the risk reduction as well as the risk difference showed variations between the clinical trials and observational studies, hence we have not gathered them together. The 95% confidence intervals of the risk reduction of the two study types overlapped, while those of the risk difference did not.

Five-year survival rate

Ten studies were included in the analysis with a total number of 1211 in the END group and 948 in the watchful-waiting group.

- *Risk ratio* (Table 4, Fig. 3) There was a significant heterogeneity among the included studies (Cochran $Q = 18.50$, $df = 9$, $p = 0.0298$, $I^2 = 51.4\%$). Under the random-effects model (REM), END was associated with a 67.3% improvement in the 5-year survival rate than those observed in the watchful-waiting group (RR = 0.673, 95% CI 0.508–0.893, $p = 0.006$). There was no evidence of publication bias on examining the funnel plot, Egger: bias = − 1.063209, $p = 0.3159$.
- *Risk difference* (Table 4) There was a significant heterogeneity among the included studies (Cochran $Q = 17.31$, $df = 9$, $p = 0.044$, $I^2 = 48.01\%$). Under the random-effects model (REM), watchful-waiting group was associated with a 5-year survival rate that was 8.6% less than that of the END group (RD = 0.0861, 95% CI 0.0314–0.141, $p = 0.002$). There was no evidence of publication bias on examining the funnel plot, Egger: bias = 0.13042, $p = 0.9303$.

Table 4 Meta-analysis for the "Five-years survival rate"

Study	Intervention	Controls	Relative risk				Risk difference			
			Relative risk	95% CI	Weight (%)		Risk difference	95% CI	Weight (%)	
					Fixed	Random			Fixed	Random
Beenken et al. [39]	2/15	63/138	0.292	0.0794–1.075	1.72	3.90	−0.323	−0.514 to −0.132	3.76	6.01
Yii et al. [40]	7/27	18/50	0.720	0.345–1.505	5.38	8.96	−0.101	−0.313 to 0.111	3.05	5.13
Capote et al. [27]	7/87	15/67	0.359	0.155–0.831	4.16	7.59	−0.143	−0.258 to −0.0284	10.38	11.28
D'Cruz et al. [41]	39/159	64/200	0.767	0.546–1.076	25.38	17.29	−0.0747	−0.168 to 0.0183	15.87	13.63
Yuen et al. [42]	4/36	5/35	0.778	0.227–2.660	1.93	4.28	−0.0317	−0.187 to 0.123	5.73	8.03
Feng et al. [47]	9/151	10/71	0.423	0.180–0.995	4.00	7.39	−0.0812	−0.171 to 0.00805	17.23	14.06
Kelner et al. [48]	67/161	19/61	1.336	0.882–2.024	16.93	15.37	0.105	−0.0343 to 0.244	7.12	9.18
Huang et al. [49]	30/151	4/22	1.093	0.426–2.804	3.29	6.45	0.0169	−0.156 to 0.190	4.57	6.91
D'Cruz et al. [28]	48/243	78/253	0.641	0.468–0.877	29.74	17.95	−0.111	−0.187 to −0.0350	23.91	15.71
Liu et al. [50]	20/181	13/51	0.433	0.232–0.810	7.47	10.81	−0.144	−0.272 to −0.0164	8.38	10.08

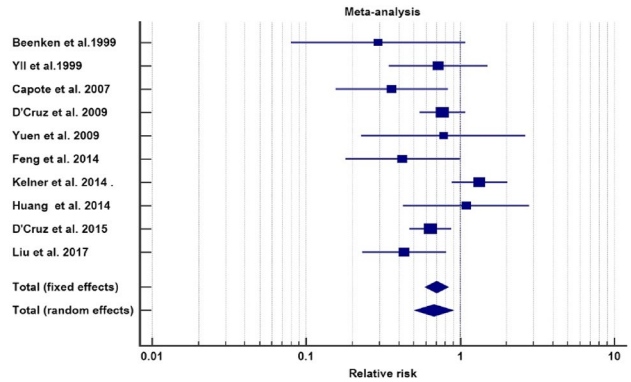

Fig. 3 Forrest plot of risk ratio for the 5-year survival rate

Discussion

The oral cavity is the most common site in the head and neck for primary malignant tumors and more than 90% of these cases are oral squamous cell carcinomas (OSCC) [1, 8]. Cervical nodal metastases is the most important prognostic factor for recurrence and survival rate, reducing the survival rate by 50%, especially with cancer of the oral tongue and floor of mouth as they have a high propensity of metastases [2, 9]. Neck staging is done clinically (bimanual palpation), radiologically and pathologically, with the latter being the most accurate way. Computed tomography (CT) and magnetic resonance imaging (MRI) are used to assess cervical lymph node metastasis; in addition, a preoperative positron emission tomography (PET) CT scan is useful as a baseline, if adjuvant treatment is anticipated. However, these imaging modalities cannot detect accurately cervical nodal micrometastasis and hence the further need for elective neck treatment [10–13]. Recently, intraoperative sentinel lymph node biopsy (SLNB) with detection of micro-RNA molecules (marker for nodal metastasis) superseded ultrasound-guided fine needle aspiration cytology (FNAC) in detecting occult nodal micro-metastasis with more accurate results [14–16].

Weiss et al. showed that observation is the ideal option when the chance of occult metastasis is less than 20% in clinically N0 (cN0) and END is preferred if the probability of occult metastasis is greater than 20% [17]. The oral tongue and floor of mouth are the two most common subsites in oral cavity to be involved with SCC; moreover, they can metastasize to the contralateral side of the neck through their midline communications [18, 19]. Therefore, those patients should be offered END even in early stage (if they are thicker than 4 mm) because they carry the highest incidence of nodal metastases and contralateral spread. Moreover, surgical resection provides pathological staging, facilitating accurate assessment [20]. Yuen et al.'s retrospective study concluded that END decreased mortality due to regional recurrence and increased the survival rate in early-stage oral tongue carcinoma [21]. However, the optimal treatment of clinically N0 neck in patients with early-stage (I and II) oral cavity SCC is still debated. Both elective neck dissection and "watchful-waiting" policy have their proponents.

Some surgeons prefer END due to a high incidence of occult nodal metastases, which if neglected will lead to poor regional control and decreased survival rate with no preoperative investigation (up till now) to be 100% sure that nodal micro-metastasis does not exist. Other surgeons mentioned that routine prophylactic neck treatment will add unnecessary cost and morbidity [7, 9]. Kligerman et al. showed that patients with early-stage carcinoma of the oral cavity (stages I and II), who have been treated with primary resection plus supraomohyoid neck dissection, developed fewer neck recurrences than those who had had resection of the primary only [22].

Shah and Andersen showed that 77% of patients with oral squamous carcinoma and clinically N0 necks at initial surveillance had pathologically adverse outcomes at the time of neck dissection. Hence, they argued for END in patients with N0 necks [23]. A meta-analysis study by Fasunla et al. [7] (including four randomized controlled articles) concluded that END reduced the risk of disease-specific death in oral cavity cancers with clinically node-negative neck. But in their study, T3 patients were included, two subsites only were assessed and follow-up duration for disease-specific death was up to 3 years only (Table 5) [7]. A recent Cochrane database update of surgical interventions for the treatment of oral and oropharyngeal cancers showed insufficient evidence to draw conclusions about END for clinically negative neck nodes at the time of removal of the primary tumor compared to therapeutic (delayed) ND [24].

Our study was conducted to evaluate the need for END versus watchful waiting in early-stage OSCC (T1N0M0/T2N0M0) with proven N0 neck. It included 24 articles (4 prospective clinical trials and 20 retrospective studies) that have been published in the last three decades. In ten articles only, we were able to extract data about the 5-year survival rate. Many studies were excluded because they did not meet the inclusion criteria. For example, Okura et al.'s study was excluded because we could not extract the number of cases that suffered from regional recurrence in each group [25]. Also, Dillon et al.'s study in 2017 was excluded because we could not extract the number of cases of early-stage oral SCC, since the authors pooled the data of early- and late-stage OSCC together [26].

Regional control

Regarding the evaluation of regional recurrence in early-stage OSCC, our meta-analysis included 24 articles (f4 randomized clinical trials and 20 retrospective studies) with a total of 219) patients who underwent END and 1619 cases

Table 5 Meta-analysis studies

	Fasunla et al. [7]	Massey et al. (2018)	Our study
Included articles	Four randomized controlled trials only	Five randomized controlled trials and 34 retrospective studies in the last four decades	Four randomized controlled trials and 20 retrospective studies in the last three decades
Included articles are those published in English language only	Yes	No	Yes
Stages I and II OSCC segregation	No	Yes	No
Oral cavity subsites included	Only oral tongue and floor of mouth	Six subsites	Six subsites
TNM stage	T1, T2 and T3/N0/M0	T1 and T2/N0/M0	T1 and T2/N0/M0

who underwent watchful waiting (therapeutic neck dissection). Meta-analysis for the four randomized "prospective" clinical trials (with a total of 343 cases in the END group and 361 cases in the watchful-waiting group) showed that END was associated with a risk of regional recurrence = 36.1% of that in the watchful-waiting group. Meta-analysis for the 20 "retrospective" studies (with a total of 1847 cases in the END group and 1258 cases in the watchful-waiting group) showed that END was associated with a risk of regional recurrence = 63.1% of the watchful-waiting group. These results confirmed the importance of END in reducing regional recurrence in early-stage OSCC with N0 neck.

5-year survival rate

Although many studies found improved survival rates in patients with early-stage OSCC and N0 neck who underwent END at the time of primary tumour resection [5, 22, 27, 28], Vandenbroucke et al. failed to show a statistically significant difference in survival rate between the group who received radical neck dissection and the group who was observed and received therapeutic neck dissection [29].

Kligerman et al. mentioned improved 3-year survival rate in early-stage OSCC who underwent END versus watchful waiting [22]. Dias et al. showed improved 3- and 5-year survival rates in patients with T1N0M0 SCC of the oral tongue and floor of the mouth who received END versus observation [30]. Goto et al. showed improved 5-year survival rate when END was done versus observation in early-stage oral tongue SCC [31]. Huang et al. mentioned similar results regarding disease-free survival (absence of loco-regional recurrence or second primary cancer) and overall survival [32]. Also, Peng et al. concluded that END led to improved disease-free survival in T1 oral tongue SCC [4].

Although Keski-Säntti et al. showed that early-stage oral tongue SCC patients who received END suffered from significantly fewer regional recurrences than the watchful-waiting group, there were no statistical differences in the overall survival and disease-specific survival between the two groups [33]. Also, Liu et al. and Zhang et al. concluded that END had not increased the disease-free survival or overall survival in clinical stage I oral tongue SCC [34, 35].

From the above, we can see that the 24 included articles in our study depended on different rates to assess survival after END and watchful waiting (3- and 5-year survival rate, overall survival, disease-specific survival and disease-free survival). Therefore, we chose the 5-year survival rate to pool its results in this meta-analysis. We gathered the results of 5-year survival rate from (10) articles with a total of 1211 of patients who underwent END versus 948 cases who underwent watchful waiting. There was a significant heterogeneity among the included articles. END was associated with a 67.3% improvement in the 5-year survival rate than those observed in the watchful-waiting group. These findings confirmed that elective neck dissection in early-stage OSCC with N0 neck can significantly improve the 5-year survival rate, hence the importance of END in early OSCC with N0 neck in reducing regional recurrence and improving the 5-year survival rate.

Limitations of the current study

- Radiologic neck staging as N0 for cervical nodal metastasis differed between the various included studies. For example, some studies depended on high-definition neck ultrasound, while others depended on CT or MRI.
- In our study, patients with stage I (T1N0M0) and stage II (T2N0M0) OSCC were pooled together, while in the meta-analysis study published by Massey et al. (2018), they were segregated. Massey et al. concluded that the incidence of occult cervical nodal metastasis in stage I and stage II OSCC were 11.5% and 24.5%, respectively. For that, they recommended END in T2N0M0 and watchful waiting in T1N0M0 OSCC [36]. However, we should be cautious while interpreting these results, since most of these studies did not use the recent TNM staging for OSCC, which incorporated the depth of invasion (DOI), being a very important prognostic factor. The 8th edition of the American Joint Committee on Cancer

(AJCC) staging manual defined T1 OSCC as a tumor size ≤ 2 cm and DOI ≤ 5 mm [37].

Conclusions

Elective neck dissection is better than watchful waiting in early (T1/T2)-stage oral cavity squamous cell carcinoma with N0 neck, regarding regional recurrence and 5-year survival rate.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest regarding the publication of this paper.

Ethical considerations All procedures performed in the included articles were in accordance with the ethical standards of the institutional and the national research committee and with the 1964 Helsinki Declaration and its later amendments.

Consent We made sure that all included articles in this study have an informed consent from all patients preoperatively.

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