Japanese Journal of
Oncology and Clinical Research

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Research Open Access

End Versus Observation in CT1-T2 Oral Tongue Squamous Cell Carcinoma – A Meta-Analysis of 11973 Patients

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Received Date: July 03, 2020 **Accepted Date:** July 23, 2020 **Published Date:** July 27, 2020

Citation: Akheel Mohammad (2020) End Versus Observation in CT1-T2 Oral Tongue Squamous Cell Carcinoma – A Meta-Analysis of 11973 Patients. JJ Oncol Clin Res 1: 1-11.

Abstract

Introduction: The surgical management of the clinical negative neck node in early oral tongue squamous cell carcinoma (OTSCC)has been the topic of debate for a few decades. As the occult cervical lymph node metastasis is considered to be the prime prognostic factor in early OTSCC, this meta-analysis has been carried out to find the risk of regional nodal recurrence, disease-specific survival, and overall survival rates in the outcome of Elective neck dissection (END) versus patients under observation.

Materials & Methods: The articles were electronically retrieved from Ovid Medline, Pub Med, Cochrane, and Scholar for comparison of END versus Observation in early OTSCC. The search strategy identified 37 relevant review articles from April 1979 to April 2020 from different search engines. A total of 11,973 patients from 32 retrospective analysis, 4 prospective and 1 randomized control trials were included in this meta-analysis.

Results: Statistical analysis revealed Overall test (OR: 5.31 95% CI: -2.132- 14.698) with t-test 1.919 and p-value 0.113 which is not statistically significant but the readings say that there is always better Disease-specific survival with END patients rather than patients kept on observation. The overall test revealed (OR: 13.02 95% CI: 1.360- 17.154) with t-test 2.382 and p-value 0.023 which is statistically significant and showed that End significantly reduced the risk of regional nodal recurrence. The overall test revealed (OR: 7.93 95% CI: -15.461- 4.238) with t-test -1.347 and p-value 0.220 which is statistically insignificant and but showed that to some extent Overall survival improves in a patient with END than the patients kept on observation

Conclusion: This meta-analysis finds that there is a statistically significant relationship when Elective neck dissection was performed which reduced the risk of regional nodal recurrence. This analysis didn't statically find any significance in Disease-specific survival and with END patients but however showed good prognosis when compared to patients kept under observation.

Introduction

Cancer is being recognized as the leading cause of morbidity and mortality after cardiovascular disease [1,2]. The most common type of oral cavity cancers are squamous cell carcinoma which constitutes approximately 90% of all cancers [3,4]. The most frequent sub-site of the lip oral cavity cancer is the tongue cancer [5]. The etiology of the oral cavity cancer is attributed to the use of tobacco and its related products, alcohol use, sedentary lifestyle, diet and nutrition, dental irritation, genetic factors & HPV infections [6]. Cervical nodal metastasis is considered as the most important prognostic factor which solely determines the survival and prognosis of patient [7,9,10,16]. It is estimated that the involvement of the lymph node in oral cavity cancers reduces the survival by 50% and the presence of extranodal extension further decreases the survival by 50% [8].

The management of the N0 neck in early tongue cancer has been the topic of discussion since the last three decades and is still a controversial topic. Surgery is the mainstay treatment of early-stage oral tongue squamous cell carcinoma (OTSCC). The decision while performing the surgery is whether to address the neck at the time of excision of the primary tumor or to observe the neck till clinical positive neck nodes. Various studies have been reported in literature favoring observation as well as Elective neck dissection (END). Neck dissection along with the excision of primary is thought to be benefitted in cases of subclinical occult metastasis [9]. The presence of a higher incidence of occult metastasis in cases of early oral cancers is approximately 16 to 36% [10-12]. The logic lies in the fact that the subclinical occult metastasis plays a pivotal role in the early OTSCC and considered to be the key factor for the loco-regional failure in the cases where the only resection of the primary tumor has been performed. Meanwhile, the quality of life is compromised in the END because of the invasiveness of neck surgery [13]. Whereas, in the "Wait & Watch" group, the observed neck is benefitted in a truly negative clinical neck as those patients experience less extensive surgery.

The aim of this study is to systematically review the current literature to (1) find disease-specific survival patients after END versus patients kept on observation (2) find the neck nodal recurrence in END patients and patients kept on Observation (3) find the overall survival rate in END patients and patients kept on observation.

Material & Methods

The data collected for this study was performed according to PRISMA guidelines. Electronic searches were performed using Ovid Medline, PubMed, Cochrane, Scopus, and Scholar from 1970 to April 2020. Search terms used to achieve maximum data were: ("squamous cell carcinoma" OR "Cancer" OR "Carcinoma" OR "SCC") AND ("Tongue" OR "oral tongue" OR "mobile tongue") AND ("T1" OR" T2" OR "early stage") AND ("elective neck dissection" OR "END", "neck dissection" OR " no neck treatment" OR "observation" OR " wait and watch") AND ("node-negative neck" OR "N0 neck") as either terms or MeSH terms. The data obtained from the above search results were reviewed and the relevant articles were selected based on the inclusion and exclusion criteria of our study.

Inclusion criteria: The articles with full text in the English language were included in the study. Only early-stage cancer as T1, T2, and N0 neck are included in the study. Randomized trials and matched Studies including the elective neck dissection versus observation were included. All patients included should be pathologically proven as Squamous cell carcinoma of the tongue without any clinically apparent lymphadenopathy or distant metastasis at the time of diagnosis. Exclusion criteria: T3 and T4 lesions of the tongue, medically compromised patients, the patient completed radiation therapy prior to surgery.

Data extraction

There were 2 reviewers in this study to discuss any difference in opinion. The first reviewer extracted all the data from the published articles. The information collected was the type of study design, year, patient characteristics (age and sex), country and period, tumor stage distribution, data on END versus observation, follow up period, and the outcome of the articles. All this information was reviewed by the second reviewer. Three parameters were chosen as endpoints for the systemic review and meta-analysis: occult cervical lymph node metastasis, neck nodal recurrence, and overall survival rate. (Table 1) shows the demographic table with a total of 37 articles was included in the study with 11,973 patients with all the data collected.

Statistics

To evaluate the heterogeneity of studies, the chi-square test (x^2) was done. The level of significance was determined for heterogeneity at p=0.05. I^2 value determined the percentage of variation across the studies. Values < 50% show less variability. For comparison between two parameters end and observed values, the t-test was applied and the level of significance was deter-

mined, along with confidence interval at 95% level.

Results

The search strategy identified 37 relevant review articles from April 1979 to April 2020 from different search engines. A total of 11,973 patients from 32 retrospective analysis, 4 prospective and 1 randomized control trials were included in this meta-analysis.

Out of 37articles, 11 articles (Table 2) were included in the meta-analysis to find Disease-specific survival for Elective neck dissection patients versus Observation. The HR test revealed that X^2 IS 30.0, I^2 is 42% with p-value 0.224. The overall test revealed (OR: 5.31 95% CI: -2.132- 14.698) with t-test 1.919 and p-value 0.113 which is not statistically significant but the readings say that there is always better Disease-specific survival with END patients rather than patients kept on observation (Figure 1).

All the 37 articles with 11,973 patients (Table 3) were included in the meta-analysis to find the nodal recurrence in END patients versus patients kept on observation. The HR test revealed that X^2 IS 394.917, I^2 is 40% with p-value 0.506. The overall test revealed (OR: 13.02 95% CI: 1.360- 17.154) with t-test 2.382 and p-value 0.023 which is statistically significant and showed that End significantly reduced the risk of regional nodal recurrence (Figure 2). Out of 37 articles, 16 articles (Table 4) were included in the meta-analysis to find the overall survival in END patients versus patients kept on observation. The HR test revealed that X^2 is 56, I^2 is 43% with p-value 0.229. The overall test revealed (OR: 7.93 95% CI: -15.461- 4.238) with t-test -1.347 and p-value 0.220 which is statistically insignificant and but showed that to some extent Overall survival improves in a patient with END than the patients kept on observation. (Figure 3).

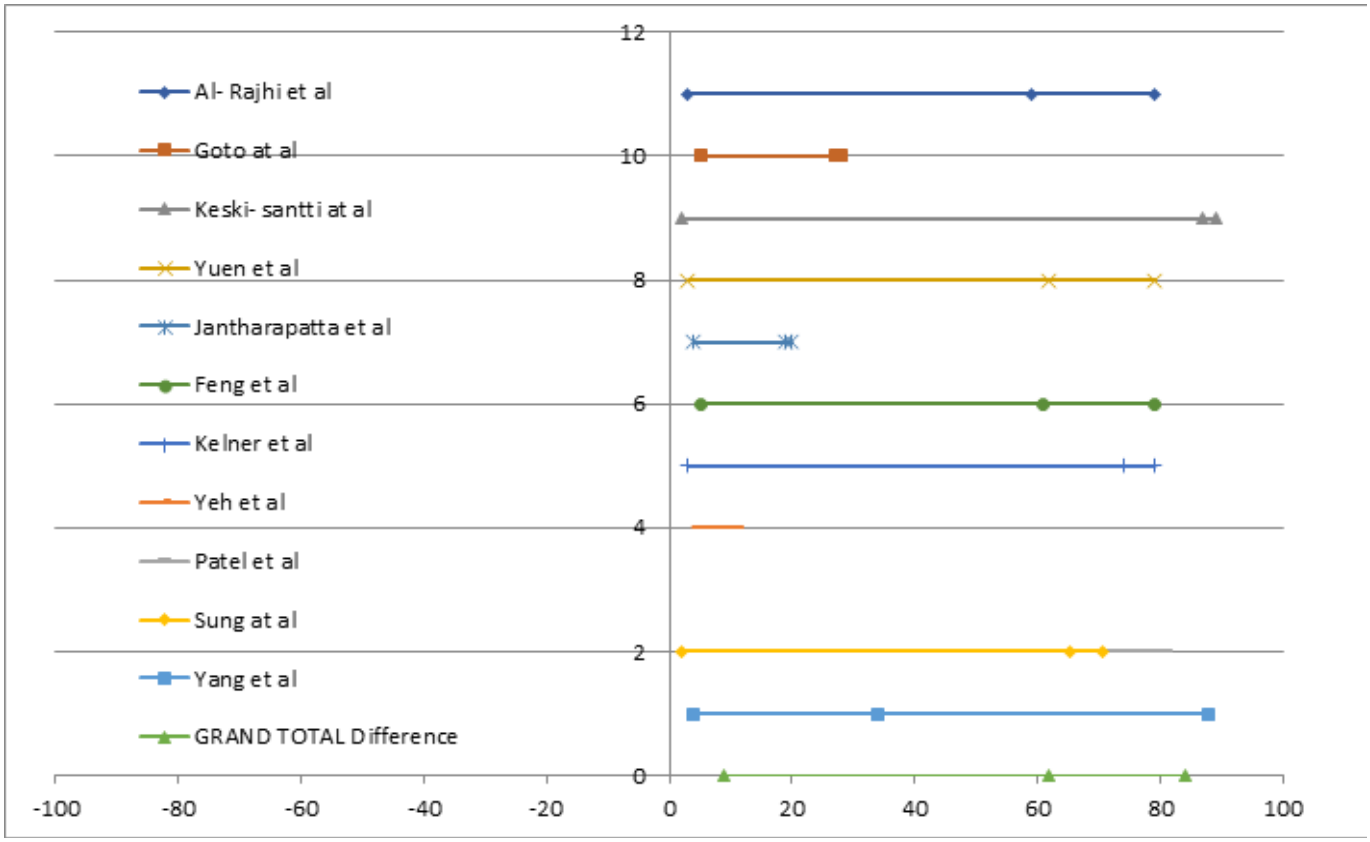

Figure 1- Tabulation of HR of all 11 articles to find Disease-specific survival for END versus patients kept on observation.

Article	Year	Design	Sex-(M/F)	Age	Country, Dates	Total Patients	Patients included in analysis	No of pts(END)	Follow up time
Fakih et al	1989	Prospective randomized	45/25	NA	INDIA (1985-1988)	70	40	30	Median 20 months)
Franceschi et al	1993	Retrospective	NA	Median 60	America (1978-1987)	211	148	63	Minimum 5yrs
Lydiatt et al	1993	Retrospective	93/63	Median (60.5/64)	America (1970-1985)	156	102	54	Median (Obs -78month / END - 67.5months)
Yuen et al	1997	Retrospective	36/27	Median 57	Hong Kong (1980-1994)	63	30	33	Median 67 months
Yii et al	1999	Retrospective	54/23	Median 57	United Kingdom (1983-1995)	71	50	13	Median 48 months
Beenken at al	1999	Retrospective	99/70	Mean 61	United states (1956-1994)	150	135	15	Median 4.8 years
Haddadin et al	1999	Retrospective	72/65	Mean 65.7	United kingdom	137	90	47	NA
Kligerman et al	2001	Retrospective	32/17	Median 59	Brazil (1985-1995)	28	17	11	Median 57 months
Kramer et al	2001	Retrospective	55/41	NA	Canada (1985-1994)	96	75	21	Minimum 5yrs
Al- Rajhi et al	2002	Retrospective	45/48	Median 60	Saudi arabia (1980-1997)	93	29	36	Median 62 months
Goto at al	2005	Retrospective	55/35	Median 50	Japan (1985-2000)	90	57	33	Median 66months)
Deng et al	2005	Retrospective	59/36	Median 50	China (1988-1997)	95	24	71	Minimum 5yrs
Keskisantti at al	2006	Retrospective	41/39	Median 57	Finland (1992-2002)	80	34	44	Minimum 2yrs
Huang at al	2008	Retrospective	325/55	Median 48	Taiwan (1995-2002)	380	56	324	Median 38months
An et al	2008	Retrospective	35/28	Mean 56	Korea (1987-2006)	63	43	20	Median 59 months
Yuen et al	2009	Prospective, randomised	43/28	Mean, OBS-58; END- 56	Hong Kong (1996-2004)	71	35	36	Median 34 months
D Cruz et al	2009	Retrospective	239/120	Median 59	India (1997-2001)	359	200	159	NA
Lin et al	2011	Retrospective	47/34	Median 63	Australia (1991-2009)	81	47	29	Median 34months
Liu et al	2011	Retrospective	79/52	Median 52	China (1991-2003)	92	43	49	NA
Li at al	2011	Retrospective	78/54	Mean61/59	China (1997-2007)	132	61	71	Median(END 4yrs/ Obs 3yrs)
Ryott et al	2011	Retrospective	NA	NA	Sweden	74	40	33	Mean 74months
Pugazhendi et al	2012	Retrospective	15male/ 6 female	NA	India (2009-2011)	21	10	11	Median 8.2months
Janthara-patta et al	2012	Retrospective	54/55	Median 64	Thailand (1992-2000)	109	68	41	Median 64
Feng et al	2014	Retrospective	104/125	Mean58.1	China (1993-2010)	229	73	156	Median 58 months

Kelner et al*	2014	Retrospective	160/61	Median 58	Brazil (1980-2010)	222	61	161	Median 68.7 months
Peng et al	2014	Retrospective	64/59	Mean 56	United states (1990-2009)	123	35	88	Median 29months
Zhang et al	2014	Retrospective	33/32	Mean 60.7	America (1999- 2007)	65	29	36	Median 56.8months
Yeh et al	2014	Retrospective	NA	Mean(54.2	Taiwan (2001-2009)	253	77	176	Median 61.9months
Mirea et al	2014	Prospective	69/17	Mean 54	Romania	86	38	48	Minimum 2yrs
D cruz et al	2015	Prospective, randomised	374/ 122	Mean 48	India (2004-2014)	496	253	243	Median 39months
Patel et al	2016	Retrospective	3951/ 3059	Mean 62.1	United States (1998-2011)	7010	4279	2720	NA
Otsura et al	2016	Retrospective	97/65	Mean 61.1	Japan (1996-2006)	152	136	26	NA
Orabona et al	2016	Retrospective	59/68	Mean 59.4	Italy	127	61	66	Mean 41.6months
Sung at al	2017	Retrospective	56/42	Mean 57	Korea (2005-2014)	98	84	14	Mean 33.7 months
Logana-than et al	2017	Retrospective	50/31	Median 57	United King-dom (2000-2006)	81	65	16	Median 32months
Gad ZS et al	2018	Retrospective	44/44	Mean 59.2%	Egypt (2007-2013)	88	13	75	54months
Yang et al	2018	RCT	122/99	Mean (51.8/54.5)	China (2008-2014)	221	110	111	Mean 44.3months

Table1: Demographic

Article	END (%)	OBSERVATION (%)
Al- Rajhi et al	79	59
Goto at al	Observation vs END, HR, 0.271 (95% CI, 0.026-2.854,NS)	
Keski- santti at al	82	77
Yuen et al	89	87
Jantharapatta et al	DSS- 2.20(0.20-19.92) 95%Cl	
Feng et al	79.2	61.9
Kelner et al*	74	79
Yeh et al	DSS- 0.83(0.11-6.45) 95%Cl	
Patel et al	Obs(T1- 0.8193, T2-0.5735); END (T1- 0.816, T2- 0.8015)	
Sung at al	70.7	65.3
Yang et al	DSS- 1.75(0.88-3.49) 95%Cl	

RESULTS	HETEROGENEITY TEST				Odd ratio	SE	95% CI	OVERALL TEST	
	X^2	df	p-value	I^2	OR			t-test	p-value
DSS	30.0	25	0.224	42%	5.31	3.27378	-2.13218-14.69884	1.919	0.113
*p-value>0.05 is insig									

Table 2: Disease specific survival for END versus patients kept on observation.

Article	OBSERVATION (%)	END
Fakih et al	23(57.5%)	9(30%)
Franceschi et al	39(26.4%)	10(15.9%)
Lydiatt et al	17(16.7%)	10(18.5%)
Yuen et al	14(46.7%)	3 (9.1%)
Yii et al	22(44%)	1(7.7%)
Beenken at al	32(23.7%)	0
Haddadin et al	38(42.2%)	8(17%)
Kligerman et al	6(35.3%)	0
Kramer et al	24(32%)	2(9.5%)
Al- Rajhi et al	11(38%)	4(11%)
Goto at al	15(26.3%)	5(15.1%)
Deng et al	6(25%)	5(7.0%)
Keski- santti at al	8(23.5%)	4(8.7%)
Huang at al	16(28.6%)	40(12.3%)
An et al	5(11.6%)	5(25%)
Yuen et al	11(31.4%)	2(5.5%)
D Cruz et al	94(47%)	9(5.7%)
Lin et al	20(42.5%)	5(17.2%)
Liu et al	10(23.2%)	8(16.3%)
Li at al	10(14.1%)	23(37.7%)
Ryott et al	16(36%)	3(10%)
Pugazhendi et al	2(20%)	0
Jantharapatta et al	12(17.6%),	23(56.1%)
Feng et al	14(19.2%)	15(9.6%)
Kelner et al*	16	21
Peng et al	2(5.7%)	7(7.9%)
Zhang et al	4(13.8%)	5(13.9%)
Yeh et al	10(24.7%)	16(9.1%)
Mirea et al	8(16.7%)	18(47.4%)
D cruz et al	108(42.7%)	25(10.3%)
Otsura et al	30(22.1%)	3(11.5%)
Orabona et al	5(8.2%)	8(12.2%)
Loganathan et al	4(25%)	6(9.2%)
Gad ZS et al	2(15.4%)	16(21.3%)
Yang et al	19(17.3%)	30(27.0%)

RESULTS	HETEROGENEITY TEST				Odd ratio OR	SE	95% CI	OVERALL TEST	
	X^2	df	p-value	I^2				t-test	p-value
NR	394.917	396	0.506	40%	13.02	3.886	1.360-17.154	2.382	0.023*
*p-value<0.05 is sig									

Table 3: Nodal recurrence in END versus Observation

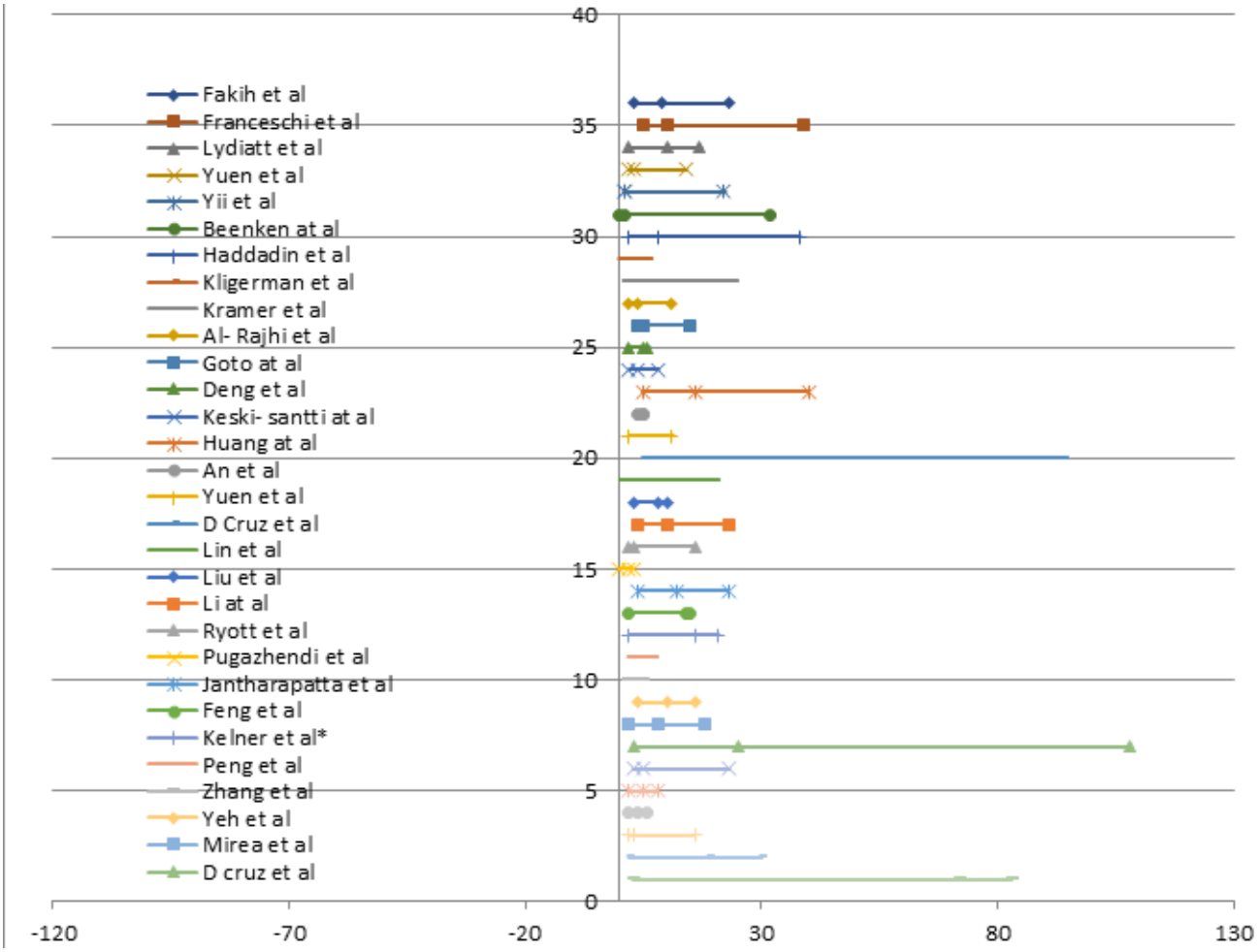

Figure 2- Tabulation of HR of all 37 articles to find Nodal recurrence in END versus Observation

Article	OBSERVATION (%)	END (%)
Yii et al	65	75
Haddadin et al	53.6	80.5
Deng et al	OS- 0.33(0.16-0.67) 95% Cl	
Keski- santti at al	66	63
Huang at al	75.1	87.2
D Cruz et al	62	69
Liu et al	75.9	83.9
Li at al	OS- 0.73(0.31-1.71)95%CL	
Jantharapatta et al	OS- 1.33(0.33-5.40) 95%Cl	
Kelner et al*	77	70
Yeh et al	OS- 1.01(0.99-1.03) 95%Cl	
D cruz et al	END vs OBSERVATION, HR 0.64(95% CI, 0.45-0.92), P =0.01	
Patel et al	Obs(T1- 77.1% , T2 -45.2%); END(T1- 77.8%, T2 - 68.8%)	
Otsura et al	OS-0.61(0.27-1.35) 95% Cl	
Orabona et al	Overall relapse free survival - Obs 34.2+/- 16.4months & END 37.9+/-15	
Sung at al	92.4	83.3
Loganathan et al	OS- 0.26(0.01-5.24) 95% Cl	

RESULTS	HETEROGENEITY TEST				Odd ratio OR	SE	95% CI	OVERALL TEST	
	X^2	df	p-value	I^2				t-test	p-value
OS	56	49	0.229	43%	7.93	4.16582	-15.46311-4.23811	-1.347	0.220
*p-value>0.05 is inside									

Table 4: Overall Survival for END and observation

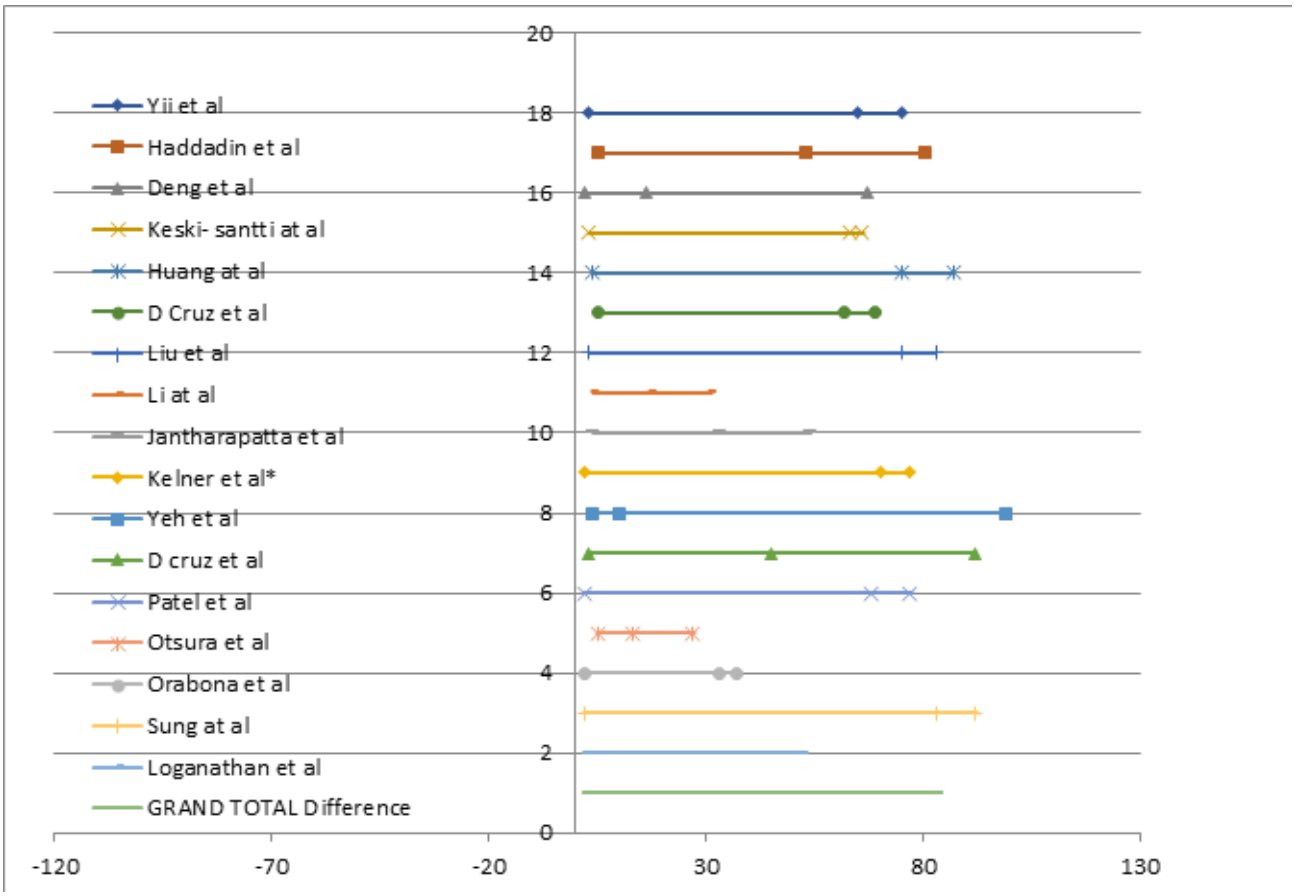

Figure 3: Tabulation of HR of all the 16 articles to find Overall Survival for END and observation

Discussion

OTSCC is a challenging entity when compared to other subsites of the oral cavity because of its unpredictable nature of lymphatic involvement. The lymphatic spread of the OTSCC can be sub-clinical at the time of diagnosis and it can be presented as unilateral or bilateral Involvement. The lymph node metastasis depends on various factors such as tumor growth type, size, differentiation, mode of Invasion, the pattern of Invasion, tumor thickness, histological grading, and stagin G [14,15]. All available preoperative and pre-surgical assessments that includes clinical neck examination by palpation and various imaging modalities like computed tomography (CT scan), magnetic resonance imaging (MRI scan), positron emission tomography–computed tomography (PET-CT scan), and ultrasonography) cannot justify the role of END as an accurate diagnostic procedure to stage the N0 neck clinically. Radiologic investigation modalities currently available have sensitivity ranging from 70 to 80% and have shown some improvements in the detection of neck nodal metastasis. Therefore, END may help in defining the status of the neck, removing subclinical or occult metastasis and determining the need for postoperative adjuvant therapy. It is clear that the incidence of delayed nodal metastases and recurrence will be comparatively higher if the nodal status was staged only by clinical palpation compared with staging by advanced imaging techniques.

The prime etiology of treatment failure and poor prognosis in early OTSCC is neck nodal recurrence [18]. According to various studies, it has been concluded that the recurrence rate of cervical lymph nodes is higher in tongue compared to other sub-site, because of the rich vascular supply, lymphatic drainage and frequent mechanical movement of the tongue [19,20]. After reviewing the literature the chances of neck node recurrence are less in END when compared with the observation. Yuen, et al. (2009) have concluded that elective neck dissection has significantly reduced neck nodal recurrence [15-17]. A study was carried out by Tsang et al suggesting that END is suitable for T2 lesions of tongue and patients kept under wait and watch policy was only considered when the tumor thickness is less than 4mm, G2 grading, and patients are ready to be in close follow up [21]. The concept of Elective neck dissection in early-stage OTSCC is followed worldwide and has gained popularity because of the increased rate of nodal recurrence in cases of the observed neck. Although, END gives more morbidity such as shoulder dysfunction, neck pain, and keloids. The disadvantage of END occurs in the case of true N0 neck which comprises approximately 70% has to undergo morbidity to prevent neck node recurrence. The ben-

efit of observation over END is that the patients with truly subclinical nodal metastasis (30-40%) have to undergo surgery but with an increased risk of morbidity [17]. Wong. et al, described the effectiveness of salvage surgery in neck nodal recurrence to be only moderately effectively with 32% of 5-year survival rate [22]. In cases of cervical metastasis, early diagnosis and management is of utmost importance, as in delayed cases the risk of extra capsular spread and multiple involvements of nodes is increased. So, it can be said that the reduced survival rate could be seen in cases of observation group [23]. Van den Berkel et al, showed that the occurrence of the neck nodal recurrence arises in less than 18 months after the first treatment. He suggested that the reason to neck nodal recurrence is the previous presence of micro-metastasis of the lymph node which went undetected clinically. With the improvement in the technology, USG-guided FNAC has high positive and negative predictive values which are proved to be better diagnostic aids in detecting the lymph node metastasis [23]. Similarly, Sentinel lymph node biopsy is also considered to be an alternative for detecting nodal metastasis [25]. A study carried out on 10 patients with early OTSCC by Sagheb et al, comparing the histopathological findings from END group to the SLNB specimen. His results showed the sensitivity and specificity rates of 75% and 100% respectively [26]. Many surgeons believe that SLNB is an alternative option for END. In present meta-analysis p-value 0.023 which is statistically significant and showed that END significantly reduced the risk of regional nodal recurrence.

In our study, we have calculated the overall survival rate of patients undergoing END and kept under observation. Our meta-analysis shows p-value 0.220 which is statistically insignificant and but showed that to some extent Overall survival improves in patients with END than the patients kept on observation. The overall survival rate is stated as a five-year survival rate, which is the percentage of people in a study or treatment group who are alive 5 years after their diagnosis. D'Cruz and his colleagues conducted a randomized trial in 2015 comparing the rates of overall survival and disease-free survival of END versus therapeutic neck dissection in node-negative oral cancer patients. His study included 596 patients of oral cavity cancer with a maximum of 85.3% cases of tongue cancer. He suggested that END showed a significantly better overall survival rate by 12.5%. They also reported more advanced nodal disease in cases of observed neck cases [27]. Ren et al, conducted a meta-analysis comparing the results END and observation with therapeutic neck dissection for nodal repalse including 5 randomized trials. 4 studies had reported on Overall survival rate. The result showed higher OS in the END group as compared to observation with a significant inter-group difference [28]. In a meta-analysis done by Abu Ghanem et al, he demonstrated less recurrence and better disease-specific survival rate in the END group compared to observation. However, they reported no significant improvement in overall survival rates [16]. Keski- Santti et al, in his study, included 80 patients of early OTSCC with clinically N0 neck demonstrated that there is no significant improvement in the overall survival rate and disease-free survival rate after undergoing END [29]. In the study of Kligerman, he showed better 3-year survival rates from 49% to 72% in END group [23]. In 2006, Yu et al reported a 100% 5-year survival rate in the END group whereas only 68.7% in patients kept under observation [30]. Yuen et al, (2009) achieved an 89% survival rate after END and 87% survival rate in the observation group which is insignificant [17]. Fakih et al, also reported an insignificant difference in overall survival rate between the hemiglossectomy group and hemiglossectomy and radical neck dissection group [31].

In our study, we also found that p-value 0.113 which is not statistically significant but the readings say that there is always better Disease-specific survival (DSS) with END patients rather than patients kept on observation. There are many studies done in literature, the one from Yookyeong Carolyn Sim et al, [32] concluded that the survival rate is lower in poor-grade or advanced TNM stages. In their study, patients with stage I and II disease showed DSS of 100%. It could be concluded that early-stage OSCC is curable, and therefore early detection is critical.

This meta-analysis finds that there is a statistically significant relationship when the END was performed which reduced the risk of regional nodal recurrence. This analysis dint statically finds any significance in DSS and OS with Elective neck dissection patients rather than patients kept on observation but however showed good prognosis when END was performed.

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