Systematic Review and Meta-Analysis

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The occult nodal metastasis rate of early tongue cancer (T1–T2)

A protocol for a systematic review and meta-analysis

Kyu Young Choi, MD, Sang Chul Park, MD, PhD, Jin Hwan Kim, MD, PhD, Dong Jin Lee, MD, PhD*

Abstract

Objectives: In this study, a meta-analysis was conducted to evaluate the occult lymph node metastasis rate in patients with early-stage (T1–T2) oral tongue squamous cell carcinoma. Also, the correlation between occult lymph node metastasis rate and T2 ratio among T1–T2 or the reported year of each study was analyzed to adjust other confound variables.

Study Design: Literature search.

Methods: A systematic computerized search of the electronic databases was carried out for articles published between January 1, 1980, and December 31, 2018, which reported occult nodal metastasis rate in T1 and T2 (separately) tongue cancer patients. Statistical analysis was performed using Comprehensive Meta Analysis version 3.3.070. Publication bias was assessed by the Egger test and Begg funnel plot method. The correlation between occult nodal metastasis rate and T2 ratio or reported year, respectively, was assessed by meta-regression analysis.

Results: From 19 studies, a total of 1567 cases were included in the meta-analysis. By random effects model, the mean occult cervical lymph node metastasis was 24.4% (95% confidence interval; 0.205–0.248). The meta-regression revealed that the T2 ratio and the reported year of the studies did not have a significant effect on the occult metastasis rate (correlation coefficient = 0.531 and 0.002, respectively, and $P = .426$ and 0.921, respectively).

Conclusion: The meta-analysis revealed that the early-stage oral tongue squamous cell carcinoma had a rate of 24.4% for occult nodal metastasis. The occult nodal metastasis rate was not significantly affected by neither T2 ratio among T1–T2 nor reported year of the studies.

Abbreviations: AJCC = American Joint Committee on Cancer, CI = confidence interval, CT = computed tomography, MRI = magnetic resonance imaging, PET-CT = positron emission tomography-computed tomography, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta- Analyses.

Keywords: meta-analysis, occult nodal metastasis rate, oral tongue cancer, reported year, T2 ratio

1. Introduction

Oral tongue and oral cavity squamous cell carcinomas have high potential for local invasion and cervical lymph node metastasis.[1,2] Because the presence of node metastasis at the time of diagnosis is considered to be the most important prognostic factor,[3–5] determination of the nodal status is essential for treatment planning. Despite development of imaging studies, such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography-computed tomography (PET-CT), ultrasonography, and along with fine needle aspiration cytology, a considerable proportion of nodal metastases remain undetected.[6–8] Although the cervical lymph nodes are usually node-negative in the early stages (T1–T2) of squamous cell carcinoma of the tongue, still, these early-stage tongue carcinomas can harbor occult nodal metastasis in which the incidence has been reported diversely between 20% and 50%.[9–12]

In the management of late-stage (stages III and IV) tongue cancer patients without nodal metastasis, elective neck dissection is definitely implemented. However, the treatment of the clinically negative neck in early stages is still a controversial issue.[9,11–14] Some authors recommend performing elective neck dissection or elective radiotherapy,[15,16] while others favor "wait and see" policy in such cases.[17] Some indicate elective neck dissection when the risk of occult nodal metastasis is greater than 20%, which is considered by various parameters such as T stage, tumor differentiation, tumor thickness, vascular invasion, and perineural invasion, etc.[18]

Most of studies have reported total number of enrolled early stage (T1–T2) tongue cancer cases and occult nodal metastasis

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The datasets generated during and/or analyzed during the current study are publicly available.

Department of Otorhinolaryngology-Head and Neck Surgery, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul, South Korea.

* Correspondence: Dong Jin Lee, 1 Singil-ro Yeongdeungpo-gu, Seoul 150-950, South Korea (e-mail: djlee@hallym.or.kr).

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rate without reporting exact number of T1 and T2, respectively. In AJCC (American Joint Committee on Cancer) 7th system, T1 included tumor 2 cm or less in greatest dimension and T2 included tumor more than 2 cm but not more than 4 cm in greatest dimension.[19] T2 oral tongue cancers are generally considered to be more aggressive than T1 and have a high chance of occult nodal metastasis than T1 cancers. For this reason, evaluation of detailed case number of T1 and T2, respectively, instead of total case number is needed. Also, the surgical skill of neck dissection has improved year over year and the concept of elective neck dissection has changed from radical neck dissection to selective neck dissection. This is the reason why one should consider reported year of each study when discussing occult metastatic rate of oral tongue cancer.

Considering the importance of the nodal metastasis in the survival of oral tongue cancer and the debates in reported nodal metastasis rate, more clear evaluation of the occult nodal metastasis is needed in the clinical practice of the cancer as well as in the study field of radiology. This study was to conduct a meta-analysis of the occult lymph node metastasis in patients with early-stage oral tongue cancer, for the first time to be reported in the literature that analyzed T1 and T2 separately. This article presents the method of the meta-analysis, the mean occult metastasis rate, and the correlation between the occult lymph node metastasis rate and T2 ratio and reported year, sequentially.

2. Materials and methods

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) guidelines. In this study, approval of ethics committee or institutional review board was not necessary because we used publicly available data. Computerized electronic search of the databases in PubMed, Embase, Cochrane Library databases, and Google Scholar for articles published in English between January 1, 1980, and December 31, 2018, was performed. After January 1, 2018, the AJCC staging system changed from 7th edition to 8th edition. So, this research excluded the studies using AJCC 8th edition published in 2018 to assure consistency. The keywords used in the search were "occult ratio," "occult nodal metastasis ratio," "early tongue cancer," "T1 T2 tongue cancer," "head and neck cancer," and "head and neck squamous cell carcinoma." Further potentially relevant articles were acquired by using the related articles function in the PubMed, and manually checking the reference lists of the obtained articles. First, the titles and abstracts of the studies were read through and irrelevant articles were excluded. Then, the full texts were reviewed and the articles that did not meet the inclusion criteria were further excluded. Inclusion criteria were randomized clinical trials, prospective or retrospective cohorts, case–control studies, and case series that evaluated the frequency of occult lymph node metastasis in T1 and T2 oral tongue squamous cell carcinoma. Only studies that analyzed the occult nodal metastasis rate in T1 and T2 tongue cancer separately were included in this study. The occult nodal metastasis rates were confirmed by histopathologic findings of the lymph nodes postoperatively, in the patients who underwent elective neck dissection that had no clinical or radiological evidence of lymph node metastasis preoperatively.

The data were extracted independently by 2 investigators (KYC and DJL) in a customized fashion. The data collected from the studies included the number of patients, exact ratio of T1 and T2 tumor, case number of elective neck dissection and occult cervical lymph node metastasis, the first author's name, and the publication year of the article (Table 1).

Meta-analysis was performed using Comprehensive Meta-Analysis version 3.3.070 (www.Meta-Analysis.com). The occult lymph node metastasis rates were obtained directly from the original articles, and the outcomes were presented as pooled event rate and their 95% confidence interval (95% CI). The weight of the individual studies was calculated by using the Mantel–Haenszel method.[20] After the heterogeneity across studies was accessed by the Cochran Q statistic and the I^2 inconsistency test, the fixed-effects model (Mantel–Haenszel method) was used for pooling homogeneous outcomes ($P \geq .05$ and $I^2 \leq 50\%$), while the random-effects model (DerSimonian–Laird method) was used for pooling heterogeneous outcomes ($P < .05$ and $I^2 > 50\%$).[21] Potential publication bias was assessed by the Egger test and Begg funnel plot.[22] To evaluate

Table 1

Characteristics of the studies included in the meta-analysis.

	Study name	Events	Sample size	Event rate	Std Err	T1/T2	T1 ratio	T2 ratio	Report year
1	Fakih 1989[23]	10	30	0.333333333	0.387298	24/46	0.342	0.658	1989
2	Yuen 1997[24]	9	33	0.272727273	0.390868	34/29	0.54	0.46	1997
3	Beenken 1999[25]	6	15	0.4	0.527046	82/87	0.485	0.515	1999
4	Yii 1999[26]	3	13	0.230769231	0.658281	32/45	0.415	0.585	1999
5	Al-Rajhi 2002[27]	6	36	0.166666667	0.447214	30/63	0.323	0.677	2002
6	Goto 2005[28]	8	33	0.242424242	0.406202	43/37	0.537	0.463	2005
7	Keski-Santti 2006[29]	15	44	0.340909091	0.31804	40/40	0.5	0.5	2006
8	An 2008[30]	5	20	0.25	0.516398	49/14	0.778	0.222	2008
9	Huang 2008[31]	33	324	0.101851852	0.183683	195/185	0.513	0.487	2008
10	De Cruz 2009[32]	32	159	0.201257862	0.197798	187/172	0.521	0.479	2009
11	Yuen 2009[33]	8	36	0.222222222	0.400892	43/28	0.606	0.394	2009
12	Lin 2011[34]	7	29	0.24137931	0.433949	68/13	0.839	0.161	2011
13	Liu 2011[35]	12	49	0.244897959	0.332205	92/0	0.999	0.001	2011
14	Feng 2014[36]	40	156	0.256410256	0.183359	109/120	0.476	0.524	2014
15	Peng 2014[37]	20	88	0.227272727	0.254374	123/0	0.999	0.001	2014
16	Zhang 2014[38]	6	36	0.166666667	0.447214	65/0	0.999	0.001	2014
17	Leandro 2014[11]	25	74	0.337837838	0.245781	42/32	0.567	0.432	2014
18	Thomas 2014[13]	61	327	0.186544343	0.141961	193/134	0.59	0.41	2014
19	Loganathan 2017[39]	29	65	0.446153846	0.249521	25/40	0.385	0.615	2017

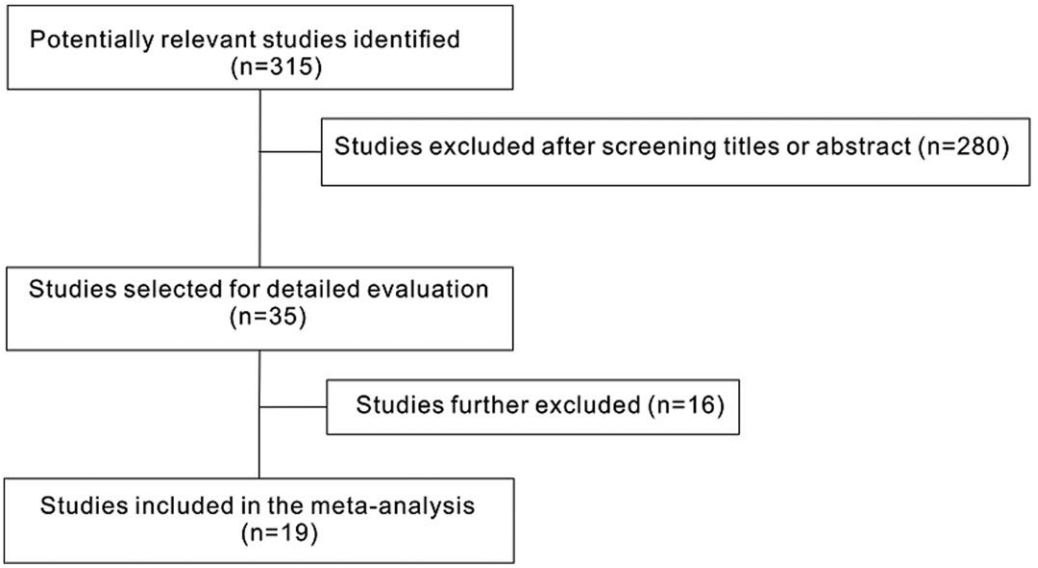

Figure 1. Flow diagram of the study selection for the meta-analysis.

the relation between occult nodal metastasis rate and T2 ratio or reported year, respectively, meta-regression analysis and calculated correlation coefficient were used. P values $< .05$ were considered statistically significant.

3. Results

The search process and the results are depicted in Figure 1. The number of the potentially related articles identified in the time period was 315 initially; however, 280 of those that did not meet the inclusion criteria of our study were excluded after assessing the titles and abstracts. Full-text review of the remaining 35 articles revealed that 16 articles had analyzed T1 and T2 tongue cancer together, so these articles were further excluded because they did not analyze T1 and T2 separately. Eventually, 19 articles that corresponded to our inclusion criteria were included in the meta-analysis.[11,13,23–39]

In the 19 enrolled studies, a total of 1567 cases were included. All studies enrolled T1 and T2 oral tongue cancer patients (with clinically negative for lymph node metastasis) that evaluated cervical lymph node metastasis by elective neck dissections. All cases had histopathologic diagnosis of squamous cell carcinoma, with at least 6 months of follow-up (mean 19.7 months, range 6–98 months). The T1 and T2 cases were analyzed separately and compared in this study. Much of the studies included T1 cases more than T2; however, 6 studies included more T2 cases and 1 included T1 and T2 evenly (Table 1).

The occult cervical lymph node metastasis rate in the 19 studies ranged from 10.2% to 44.6%, and the mean occult metastasis rate was calculated as 24.4% [95% confidence interval (95% CI) 0.205–0.248] (Fig. 2). The heterogeneity across studies accessed by the Cochran Q statistic and the I^2 inconsistency test revealed significant between-study heterogeneity ($I^2 = 71.1\%$, $P < .001$, Table 2). As a result, a random effects model was used for this meta-analysis. The meta-analysis revealed that in 24.4% of early T stage tongue cancer patients who are clinically negative for lymph node metastasis, had actually have micro-metastasis in the cervical lymph nodes, so elective neck dissection should be considered and may provide benefit for nodal recurrence and further survival in that patients. The P-value of Egger test ($P = .475$) and the funnel plots for the event rates (symmetry) (Fig. 3) indicated that there was no evidence of publication bias. The meta-regression for the T2 ratio and report year revealed no significance (correlation coefficient = 0.531 and 0.002, respectively, and $P = .426$ and .921, respectively), indicating that the T2 ratio and the reported year of the studies did not have significant effect on the occult metastasis rate (Fig. 4A, 4B and Table 3). Consequentially, by analyzing T1 and T2 separately, it was revealed that even the studies that included more T1 cases than T2, the occult metastasis rate was not significantly different from the studies with more T2 cases than T1, which means that delicate observation is needed even in minor cases.

4. Discussion

Squamous cell carcinoma of the tongue is known as the most common malignant neoplasm arising in the oral cavity.[40] Because of high potential for local invasion and regional lymph node metastasis,[1,2,41] elective neck dissection is commonly performed even in early stages of tongue cancer as well as in advanced cases.[12] The presence of cervical lymph node metastasis is usually evaluated in the treatment planning; however, occult nodal metastasis cannot be completely addressed clinically before surgical treatment of the neck. To improve locoregional control and survival, elective neck dissection of the N0 neck is commonly performed even in the early stages of tongue cancer[42]; however, the benefit is still in much debate. If the micro-metastasis of the cervical lymph node can be well addressed before treatment, unnecessary surgery can be avoided; however, it cannot be fully realized still.

With improving technology, including sectional imaging techniques, CT, MRI, and PET-CT now play an essential role in the management of head and neck cancer patients. However, the reported accuracies of these studies in determining the presence or absence of metastatic cervical lymph nodes are inconsistent, although the accuracies of these imaging studies

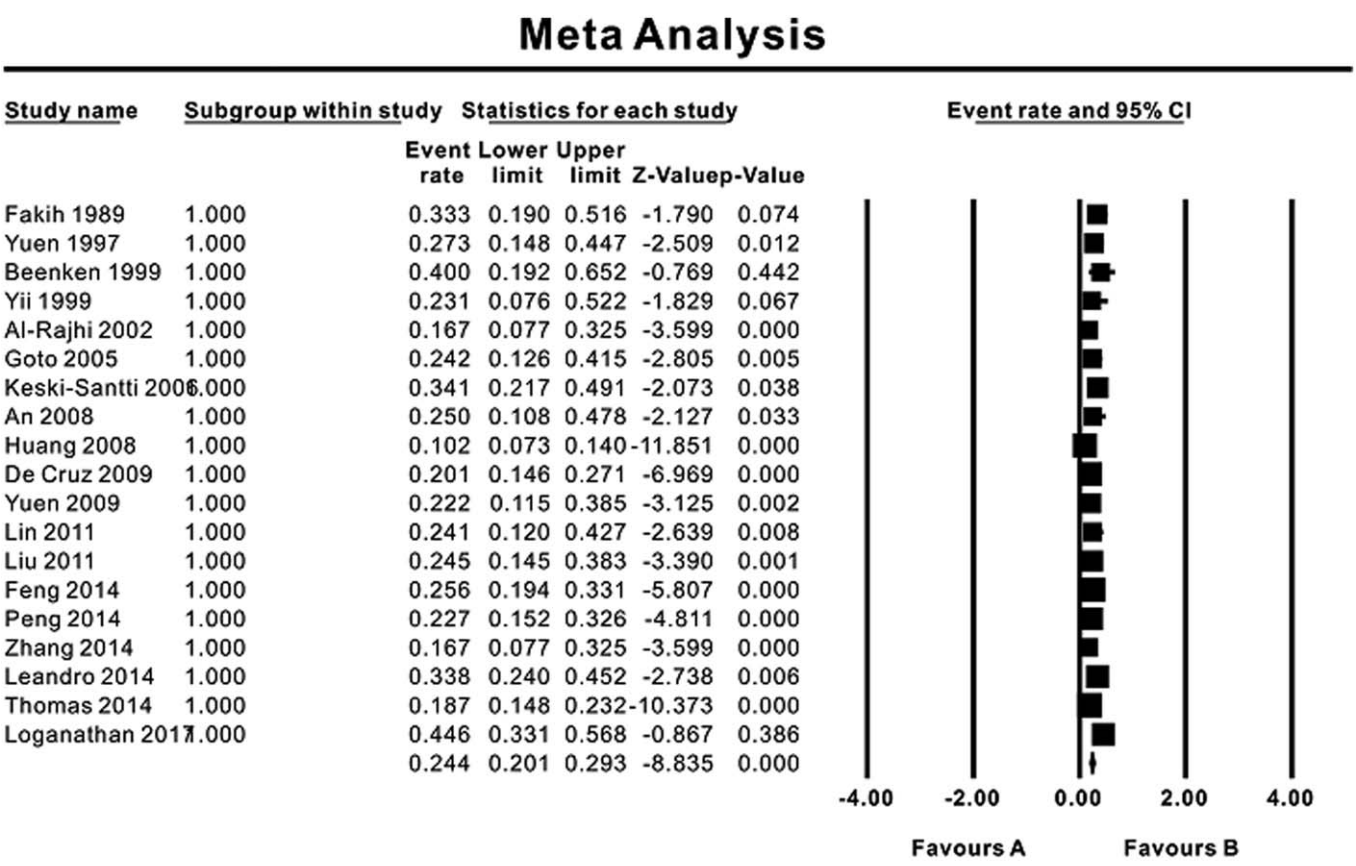

Figure 2. Forest plot for meta-analysis of occult nodal metastasis rate of early oral tongue cancer.

should be fully acknowledged preoperatively. Furthermore, micro-metastasis to cervical lymph nodes are difficult to determine clinically even with the recent techniques, and the occult nodal metastasis rates have been reported up to 20% to 50% in the literature.[9–12] Ahmed et al[5] have reported that if the tumor thickness is greater than 5 mm, 69% of early tongue cancer patients had occult cervical metastasis, while 100% of the patients with tumor thicknesses less than 5 mm had no cervical nodal metastasis.

However, recent studies report promising methods that improve diagnostic accuracies in detecting tumor metastasis. In 2018, Yavari[43] reported an effective labeling of tumor angiogenesis using monoclonal antibody avastin with 153Sm. Also, anthropomorphic phantoms of the head and neck can be used for CT scans, which reduce radiation risk while maintaining image quality.[44] However, in the study by Osipov et al,[45] diagnostic exposure of PET-CT did not reveal significant effect on mortality.

In this study, the rate of occult cervical lymph node metastasis in patients with T1 and T2 oral tongue squamous cell carcinoma was evaluated with meta-analysis. The results show that almost a quarter of early tongue cancer patients who did not have neck node metastasis clinically had harbored microscopic cancer metastasis to the cervical lymph nodes. To our knowledge, this is the first meta-analysis that evaluated occult nodal metastasis rate in early T stage (T1 and T2) tongue cancer from the studies that had addressed T1 and T2 tongue cancer cases separately, while most of the previous studies had calculated occult nodal metastasis rate from combined T1 and T2 cases. The meta-analysis result 24.4% was not beyond boundary from the

Table 2

Random effects model showing significant between-study heterogeneity.

		Effect size and 95% interval			Test of null (2-Tail)		Heterogeneity			
Model	**Number Studies**	**Point estimate**	**Lower limit**	**Upper limit**	***Z*-value**	***P***	**Q-value**	**df (Q)**	***P***	I^2
Fixed	19	0.225488	0.20466	0.247776	−19.5903	0	62.19867	18	8.99×10^{-7}	71.06047
Random effects	19	0.24408	0.200815	0.293245	−8.83537	0				

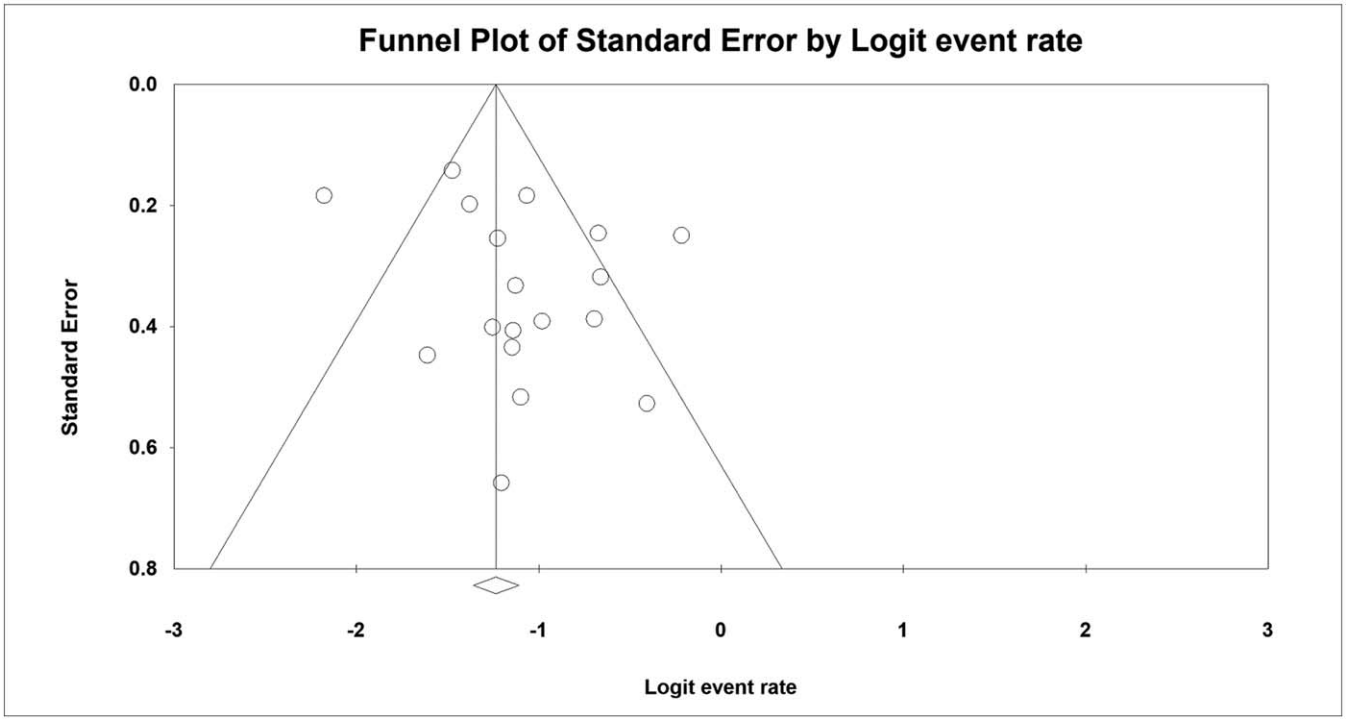

Figure 3. Funnel plot for publication bias.

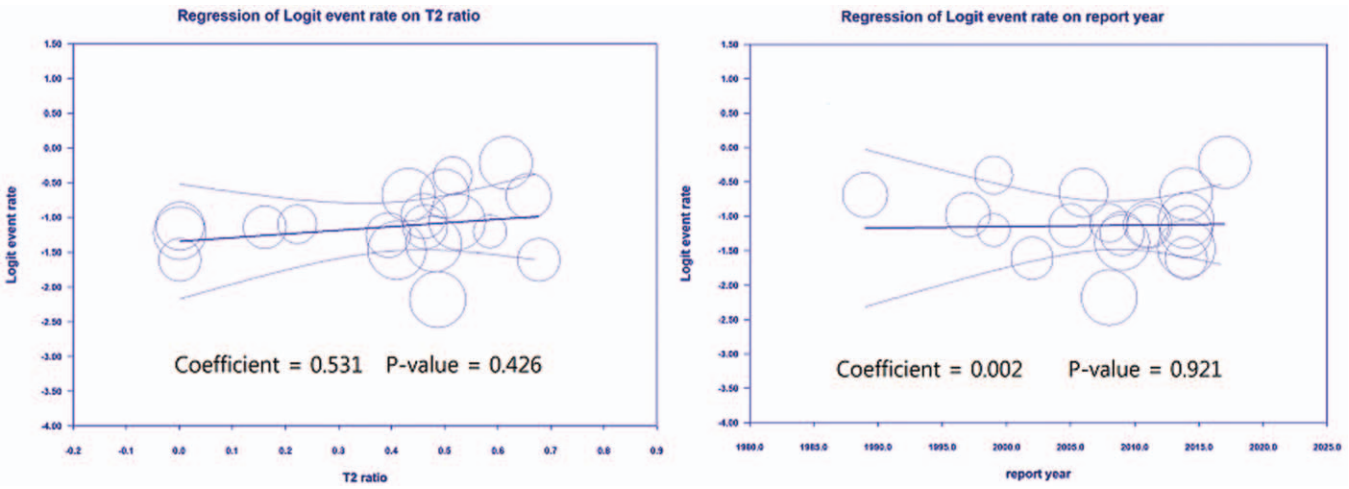

Figure 4. Meta-regression analysis including T2 ratio and reported year. (A) Scattered plot according to T2 ratio and occult metastasis rate (adjusted reported year). Fig4B showed scattered plot according to reported year and occult metastasis rate (adjusted T2 ratio).

Table 3

Meta-regression including T2 ratio and reported year (adjusted between T2 ratio and reported year).

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	*Z*-value	2-sided *P*
Intercept	−5.3062	40.3047	−84.3019	73.6895	−0.13	.8953
T2 ratio	0.531	0.6673	−0.7769	1.839	0.8	.4262
report year	0.002	0.02	−0.0373	0.0412	0.1	.9215

previous reported occult metastasis rates in the literature (20–50%).

This study puts an emphasis on the uncombined T1 and T2 case numbers assuming that the ratio of T1 or T2 cases can influence the occult nodal metastasis rate, that is, the metastasis rate might be low if the ratio of T1 cases was high and the rate might increase in the studies that had more T2 cases. However, the meta-regression analysis for the T1 and T2 ratio revealed that that the T1 or T2 ratio did not have significant effect on the occult metastasis rate. Furthermore, to evaluate whether the current improvement in imaging techniques and surgical techniques had influenced the rate of the occult cervical nodal metastasis, meta-regression analysis of the reported year of the studies was also performed in the meta-analysis. Interestingly, the reported year of the studies included was not significantly associated with the occult metastasis rate.

Knowing the occult cervical lymph node metastasis rate can be meaningful in managing head and neck cancer patients because the treatment of N0 neck in the early stages of tongue cancer patients is a controversial issue. Some clinicians recommend performing elective neck dissection (or radiotherapy),[15,16] while others favor observation.[17] Recently, however, Abu-Ghanem et al[46] have reported in their meta-analysis of elective neck dissection versus observation in early tongue squamous cell carcinoma (T1–T2) that elective neck dissection can significantly reduce the rate of nodal recurrence and improve disease free survival compared with observation.

There are several limitations in this meta-analysis. One is that most of the included studies had been retrospectively carried out and included relatively small sample sizes. Second, because of the limited number of cases, subgroup analyses of T1 and T2 separately could not be done in this study. Lastly, although the occult metastasis rate was evaluated that elective neck dissection is benefitted in 24.4% of early T stage tongue cancer patients cannot be made as a conclusion. Further long-term clinical trials with larger sample size are required to confirm these results and to better analyze the occult nodal metastasis rate of early-stage oral tongue squamous cell carcinoma.

5. Conclusion

Metastasis to the cervical lymph nodes should be identified before managing oral tongue cancer patients; however, the reported occult nodal metastasis rate in early stage (T1–T2) oral tongue squamous cell carcinoma varies among reported studies. The meta-analysis findings in this study revealed that the early-stage oral tongue squamous cell carcinoma had a rate of 24.4% for occult nodal metastasis. The occult nodal metastasis rate was not significantly affected by neither T2 ratio nor reported year, in the meta-analysis of the T1 and T2 groups separately, for the first time to be reported in the literature. Limitations exist in concluding that elective neck dissection is benefit in 24.4% of early T stage tongue cancer patients; however, this study emphasizes that subgroup analysis according to T1 and T2 stage or reported year is not needed when discussing occult nodal metastasis rate of early-stage tongue cancer. The occult nodal metastasis evaluated by this meta-analysis can be furthermore applied to the management of the oral tongue cancer patients clinically, and to the development of treatment options for such diseases. In the future, further long-term clinical trials with larger sample size can be used to offer effective treatment options in early-stage oral tongue squamous cell carcinoma, investigating approaches to improve survival of the disease.

Author contributions

Conceptualization: Kyu Young Choi, Dong Jin Lee.
Data curation: Kyu Young Choi, Sang Chul Park, Jin Hwan Kim, Dong Jin Lee.
Formal analysis: Kyu Young Choi, Sang Chul Park, Jin Hwan Kim, Dong Jin Lee.
Funding acquisition: Dong Jin Lee.
Investigation: Kyu Young Choi, Sang Chul Park, Jin Hwan Kim, Dong Jin Lee.
Methodology: Sang Chul Park, Jin Hwan Kim, Dong Jin Lee.
Project administration: Kyu Young Choi.
Software: Kyu Young Choi.
Supervision: Jin Hwan Kim, Dong Jin Lee.
Validation: Sang Chul Park, Dong Jin Lee.
Writing – original draft: Kyu Young Choi, Sang Chul Park.
Writing – review & editing: Sang Chul Park, Dong Jin Lee.

References

[1] Noorlag R, Boeve K, Witjes MJ, et al. Amplification and protein overexpression of cyclin D1: predictor of occult nodal metastasis in early oral cancer. Head Neck 2017;39:326–33.
[2] Oc P, Pillai G, Patel S, et al. Tumour thickness predicts cervical nodal metastases and survival in early oral tongue cancer. Oral Oncol 2003;39:386–90.
[3] Yuen AP, Lam KY, Chan AC, et al. Clinicopathological analysis of elective neck dissection for N0 neck of early oral tongue carcinoma. Am J Surg 1999;177:90–2.
[4] Feng Z, Li JN, Li CZ, et al. Elective neck dissection versus observation in the management of early tongue carcinoma with clinically node-negative neck: a retrospective study of 229 cases. J Craniomaxillofac Surg 2014;42:806–10.
[5] Ahmed SQ, Junaid M, Awan S, et al. Frequency of cervical nodal metastasis in early-stage squamous cell carcinoma of the tongue. Int Arch Otorhinolaryngol 2018;22:136–40.
[6] Norling R, Grau C, Nielsen MB, et al. Radiological imaging of the neck for initial decision-making in oral squamous cell carcinomas: a questionnaire survey in the Nordic countries. Acta Oncologica 2012;51:355–61.
[7] Christensen A, Bilde A, Therkildsen MH, et al. The prevalence of occult metastases in nonsentinel lymph nodes after step-serial sectioning and immunohistochemistry in cN0 oral squamous cell carcinoma. Laryngoscope 2011;121:294–8.
[8] Schroeder U, Dietlein M, Wittekindt C, et al. Is there a need for positron emission tomography imaging to stage the N0 neck in T1-T2 squamous cell carcinoma of the oral cavity or oropharynx? Ann Otol Rhinol Laryngol 2008;117:854–63.
[9] Pentenero M, Gandolfo S, Carrozzo M. Importance of tumor thickness and depth of invasion in nodal involvement and prognosis of oral squamous cell carcinoma: a review of the literature. Head Neck 2005;27:1080–91.
[10] Po Wing Yuen A, Lam KY, Lam LK, et al. Prognostic factors of clinically stage I and II oral tongue carcinoma: a comparative study of stage, thickness, shape, growth pattern, invasive front malignancy grading, Martinez-Gimeno score, and pathologic features. Head Neck 2002; 24:513–20.
[11] Matos LL, Manfro G, Santos RV, et al. Tumor thickness as a predictive factor of lymph node metastasis and disease recurrence in T1N0 and T2N0 squamous cell carcinoma of the oral tongue. Oral Surg Oral Med Oral Pathol Oral Radiol 2014;118:209–17.
[12] Dik EA, Willems SM, Ipenburg NA, et al. Watchful waiting of the neck in early stage oral cancer is unfavourable for patients with occult nodal disease. Int J Oral Maxillofac Surg 2016;45:945–50.
[13] Mucke T, Mitchell DA, Wagenpfeil S, et al. Incidence and outcome for patients with occult lymph node involvement in T1 and T2 oral

squamous cell carcinoma: a prospective study. BMC cancer 2014; 14:346.
[14] Agarwal SK, Arora SK, Kumar G, et al. Isolated perifacial lymph node metastasis in oral squamous cell carcinoma with clinically node-negative neck. Laryngoscope 2016;126:2252–6.
[15] Cunningham MJ, Johnson JT, Myers EN, et al. Cervical lymph node metastasis after local excision of early squamous cell carcinoma of the oral cavity. Am J Surg 1986;152:361–6.
[16] Wolff KD, Follmann M, Nast A. The diagnosis and treatment of oral cavity cancer. Dtsch Arztebl Int 2012;109:829–35.
[17] Orabona GD, Bonavolonta P, Maglitto F, et al. Neck dissection versus "watchful-waiting" in early squamous cell carcinoma of the tongue our experience on 127 cases. Surg Oncol 2016;25:401–4.
[18] Weiss MH, Harrison LB, Isaacs RS. Use of decision analysis in planning a management strategy for the stage N0 neck. Arch Otolaryngol Head Neck Surg 1994;120:699–702.
[19] Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471–4.
[20] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719–48.
[21] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[22] Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002.
[23] Fakih AR, Rao RS, Borges AM, et al. Elective versus therapeutic neck dissection in early carcinoma of the oral tongue. Am J Surg 1989;158:309–13.
[24] Yuen AP, Wei WI, Wong YM, et al. Elective neck dissection versus observation in the treatment of early oral tongue carcinoma. Head Neck 1997;19:583–8.
[25] Beenken SW, Krontiras H, Maddox WA, et al. T1 and T2 squamous cell carcinoma of the oral tongue: prognostic factors and the role of elective lymph node dissection. Head Neck 1999;21:124–30.
[26] Yii NW, Patel SG, Rhys-Evans PH, et al. Management of the N0 neck in early cancer of the oral tongue. Clin Otolaryngol Allied Sci 1999;24:75–9.
[27] Al-Rajhi NM, Khafaga YM, Saleem M, et al. A study comparing different approaches in managing neck nodes in early carcinoma of the tongue. Saudi Med 2002;23:1343–6.
[28] Goto M, Hasegawa Y, Terada A, et al. Prognostic significance of late cervical metastasis and distant failure in patients with stage I and II oral tongue cancers. Oral Oncol 2005;41:62–9.
[29] Keski-Santti H, Atula T, Tornwall J, et al. Elective neck treatment versus observation in patients with T1/T2 N0 squamous cell carcinoma of oral tongue. Oral Oncology 2006;42:96–101.
[30] An SY, Jung EJ, Lee M, et al. Factors related to regional recurrence in early stage squamous cell carcinoma of the oral tongue. Clin Exp Otorhinolaryngol 2008;1:166–70.
[31] Huang SF, Kang CJ, Lin CY, et al. Neck treatment of patients with early stage oral tongue cancer: comparison between observation, supraomohyoid dissection, and extended dissection. Cancer 2008;112:1066–75.
[32] D'Cruz AK, Siddachari RC, Walvekar RR, et al. Elective neck dissection for the management of the N0 neck in early cancer of the oral tongue: need for a randomized controlled trial. Head Neck 2009;31:618–24.
[33] Yuen AP, Ho CM, Chow TL, et al. Prospective randomized study of selective neck dissection versus observation for N0 neck of early tongue carcinoma. Head Neck 2009;31:618–24.
[34] Lin MJ, Guiney A, Iseli CE, et al. Prophylactic neck dissection in early oral tongue squamous cell carcinoma 2.1 to 4.0 mm depth. Otolaryngol Head Neck Surg 2011;144:542–8.
[35] Liu TR, Chen FJ, Yang AK, et al. Elective neck dissection in clinical stage I squamous cell carcinoma of the tongue: does it improve regional control or survival time? Oral Oncol 2011;47:136–41.
[36] Feng Z, Li JN, Niu LX, et al. Supraomohyoid neck dissection in the management of oral squamous cell carcinoma: special consideration for skip metastases at level IV or V. J Oral Maxillofac Surg 2014;72:1203–11.
[37] Peng KA, Chu AC, Lai C, et al. Is there a role for neck dissection in T1 oral tongue squamous cell carcinoma? The UCLA experience. Am J Otolaryngol 2014;35:741–6.
[38] Zhang T, Lubek JE, Salama A, et al. Treatment of cT1N0M0 tongue cancer: outcome and prognostic parameters. J Oral Maxillofac Surg 2014;72:406–14.
[39] Loganathan P, Sayan A, Hsu DWK, et al. Squamous cell carcinoma of the anterior tongue: is tumour thickness an indicator for cervical metastasis? Int J Oral Maxillofac Surg 2017;46:407–12.
[40] Iype EM, Sebastian P, Mathew A, et al. The role of selective neck dissection (I-III) in the treatment of node negative (N0) neck in oral cancer. Oral Oncol 2008;44:1134–8.
[41] Keski-Santti H, Kontio R, Tornwall J, et al. Sentinel lymph node biopsy or elective neck dissection for patients with oral squamous cell carcinoma? Eur Arch Otorhinolaryngol 2008;265:S13–7.
[42] D'Cruz AK, Vaish R, Kapre N, et al. Elective versus therapeutic neck dissection in node-negative oral cancer. N Engl J Med 2015;373: 521–9.
[43] Yavari K. Anti-angiogenesis therapy of cancer cells using 153Sm-Bevasesomab. ESJ 2018;2:130–9.
[44] Gómez AML, Santana PC, Mourão AP. Dosimetry study in head and neck of anthropomorphic phantoms in computed tomography scans. Scimed J 2020;2:38–43.
[45] Osipov M, Vazhenin A, Kuznetsova A, et al. PET-CT and occupational exposure in oncological patients. Scimed J 2020;2:63–9.
[46] Abu-Ghanem S, Yehuda M, Carmel NN, et al. Elective neck dissection vs observation in early-stage squamous cell carcinoma of the oral tongue with no clinically apparent lymph node metastasis in the neck: a systematic review and meta-analysis. JAMA Otolaryngol Head Neck Surg 2016;142:857–65.