

Tumor Thickness and Cervical Nodal Metastasis in N₀ Oral Tongue Squamous Cell Carcinoma Patients: A Prospective Study

Research Article

Samer issa¹, Omar Heshmeh², Issam Alameen³, Zuhair Al-Nerabieah^{4*}¹ PhD Candidate, Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Damascus University.² Professor, Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Damascus University.³ Professor, Department of Otolaryngology, Faculty of Medicine -Al Mouwasat University Hospital- Damascus University.⁴ PhD Candidate, Department of Pediatric Dentistry, Faculty of Dentistry, Damascus University, Damascus, Syria

Abstract

Background: Tumor Thickness (TT) plays an important role in the progress and prognosis of malignant tumors in general and oral squamous cell carcinoma in particular. Many studies have concluded that thicker tumors were associated with higher incidence of regional lymph node metastasis and as a result were associated with more lower survival rates.

Aim of Study: This study aimed to evaluate relation between tumor thickness (TT) and regional lymph node metastasis in oral tongue squamous cell carcinoma patients, and to evaluate (TT) as a prognostic factor for lymph node metastasis and as an influencer in the suggested treatment plan.

Materials and Methods: The study sample contained 40 patients (23 male, 17 female), who were diagnosed with stage I/II oral tongue squamous cell carcinoma. A surgical procedure for tumor excision and an excisional biopsy was performed. The tumor thickness was measured by one pathologist and the regional lymph nodes status was evaluated pathologically or radiologically or by the two methods. The study sample was divided into three groups according to tumor thickness: TT<3mm, TT (3-6mm), and TT>6mm, and the incidence of regional node metastasis in the three studied thickness groups was calculated. Tumor thickness values were compared in cases of positive regional lymph node involvement and negative regional node involvement using t-test.

Results: Regional lymph node metastasis had occurred in 14 patients of our whole sample (35%) and the rates of nodal involvement in the groups of thickness <3mm, 3-6mm, and >6mm were 18.18%, 33.33%, and 47.05% respectively. The mean tumor thickness was 8.07mm in the positive lymph nodes group and 4.96 mm in the negative lymph node group with statistically significant difference at p-value<0.05.

Conclusion: There was a higher incidence of regional lymph node metastasis in patients with thicker oral tongue SCC tumors, also there was a critical high incidence of nodal involvement in OTSCC tumors that exceeded 3mm thick. Prophylactic neck dissection or irradiation and close monitoring should be considered for those patients with more than 3mm thick tongue tumors.

Keywords: Oral Tongue Cancer; Lymph Node Metastasis; Tumor Thickness.

Introduction

The majority of oral cavity cancers affects the lower parts of mouth and especially tongue margins and the neighboring floor of mouth extending backwards to oropharynx. Oral tongue squamous cell carcinoma (OTSCC) is one of the most common types of oral cancers. It represents 25- 50% of oral cavity cancers and includes only the lesions of the anterior two thirds of tongue. [1,

2].

Tongue SCC (TSCC) is considered one of the most aggressive types of OSCC. It tends to develop regional lymph node metastasis earlier and with more incidence compared with the most other kinds of OSCC, [3-6] also it has in its early stages the larger mortality rates among various kinds of OSCC. [7]

*Corresponding Author:

Zuhair Al-Nerabieah,
PhD Candidate, Department of Pediatric Dentistry, Faculty of Dentistry, Damascus University, Damascus, Syria
E-mail: Zuhairmajid@gmail.com

Received: October 05, 2021

Accepted: October 28, 2021

Published: November 03, 2021

Citation: Samer Issa, Omar Heshmeh, Issam Alameen, Zuhair Al-Nerabieah. Tumor Thickness and Cervical Nodal Metastasis in N₀ Oral Tongue Squamous Cell Carcinoma Patients: A Prospective Study. *Int J Dentistry Oral Sci.* 2021;8(11):4897-4901. doi: <http://dx.doi.org/10.19070/2377-8075-21000990>

Copyright: Zuhair Al-Nerabieah©2021. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

TNM classification system for tumors staging has been founded on for many decades. It has formed the reference for clinicians and pathologists in determining the disease stage and prognosis and has provided the standard guidelines for tumors treatment. [8] Clinical practice has demonstrated some deficiency in this classification. There were many failure cases that were encountered when the suggested TNM treatment plan was applied, in addition to that there were some N0 cases of OSCC which did not respond -as expected- to the standard treatment plan determined according to this classification. This opinion was supported by many clinical studies which have confirmed the TNM classification deficiency in predicting cervical node metastasis, disease recurrence and survival. [9-15] and have concluded the presence of many other prognostic factors - other than tumor size - that influence the disease progression and prognosis such as tumor thickness (TT) or depth of invasion (DOI), tumor differentiation grade, perineural invasion, and many other factors.[16-20]

Many recent studies have confirmed on the role of tumor thickness or depth of invasion in predicting OSCC regional lymph node metastasis [21-24]. According to these studies the increase in tumor thickness is associated with higher incidence of regional lymph node metastasis. The minute knowledge of the role of tumor thickness in predicting nodal metastasis in TSCC patients could be resulted in much more control of the disease and as a result much more survival for those patients by revising the TNM suggested treatment plan which could be included in some cases more additional prophylactic procedures and a modified follow-up regime, so that in cases of large thickness TSCC tumors the treatment plan may include an elective neck dissection or irradiation or at least more close follow-up procedures.[10, 25]

The relation between tumor thickness and nodal metastasis in OSCC patients has been explored in many studies. [21, 23, 24] Concerning tongue SCC, most of this studies have evaluated tongue SCC as a part of a sample population based on OSCC patients, and few studies evaluated tongue SCC in particular, so that the relation between tumor thickness and nodal involvement in TSCC patients still need more studying as every subtype of OSCC has its specific characteristics related to tumor nature, clinical behavior, and disease development and prognosis. This aforementioned reason makes the studying of each subtype of OSCC separately an issue of great importance.[20, 25]

Material and Methods

A prospective study was carried out on patients with initial diagnosis of stage I/II oral tongue SCC who were accepted for treatment at Al Moasat Hospital - Damascus University – in the period between 2016 and 2020. Initially all patients suspected to have Oral Tongue SCC had the routine clinical and radiological examination for tumor diagnosis and staging.

There were forty patients with OTSCC who had met our inclusion criteria and were included in our prospective study sample. All patients included in the study underwent a radiological examination consisted of plain radiographs, sonography, CT scan and -when needed- MRI.

All patients underwent a surgical procedure for tumor excision (partial glossectomy) and an excisional biopsy was obtained and

studied by the same pathology lab. The histological grade and the maximum tumor thickness were determined by the pathologist depending on the followed standard histological criteria.

Initially we excluded all patients suffering from recurrent or previously treated tumors or suffering from tumor metastasis that had affected the regional nodes or extended beyond it such as patients with distant organs metastasis or patients with end-stage tumors. Patients with predictive factors –other than tumor thickness- that known to influence the incidence of regional lymph nodes metastasis were also excluded of our sample such as patients with T3, T4 tumors, patients with histological grade III tumors, and patients with pathologically confirmed perineural or angiolymphatic vessels invasion because of the high probability of these types of tumors to develop regional lymph node metastasis.

On the other hand, all patients with exophytic type tumors and all cases that had been diagnosed as carcinoma in situ were also excluded because of the low probability of these tumors to develop regional lymph node metastasis.

The study sample was divided into two groups depending on the presence of regional lymph node metastasis:

- 1-Patients with positive lymph node metastasis (N+).
- 2-Patients with negative lymph node metastasis (N-).

Also, the study sample was divided into three groups according to the maximum tumor thickness:

- 1-Group 1: Patients with tumor thickness <3 mm.
- 2-Group 2: Patients with tumor thickness 3-6 mm.
- 3-Group 3: Patients with tumor thickness >6 mm.

Regional lymph nodes status was determined depending on either neck dissection and consequent pathological study performed on the surgically obtained nodes specimen or on consequent radiological and pathological findings obtained during the follow-up period. The regional lymph nodes were considered positive (N+) if the pathological result of neck dissection was positive or if there was a new radiologically or pathologically confirmed lymph node metastasis that had occurred during the follow-up period.

All patients included in our study were followed-up clinically and radiologically and when needed histologically for a minimum period of 16 months. During the follow-up period all patients suffered from new regional lymph node metastasis were classified in the positive nodal group (N+), on the other hand all patients who did not suffer from new regional lymph node metastasis were classified in the negative nodal group (N-).

When the clinical and radiological and histological examinations were accomplished the TNM staging was established and the standard therapy was offered for all study patients which contained the surgical therapy alone or accompanied by one or more one kind of treatments (radio or chemo therapy).

Statistical analysis was performed using computed program SPSS Statistics software (Ver 23: IBM, Armonk, NY, USA). T-test was used to analyze the difference in tumor thickness values between the two studied nodal groups, with all statistics were considered significant at p value<0.05.

Results

40 patients with stage I/II OTSCC were included in our study (23 male, 17 female) with a mean age 65.3 years (range: 42 - 80 years). All patients underwent a surgical procedure for tumor excision with or without neck dissection and were followed-up for a mean period of 28 months (range:16.- 38 months).

The surgical procedure consisted of partial glossectomy, and the decision of associated neck dissection was taken depending on patient's clinical and histological findings. Neck dissection was performed if there was an evident risk of subclinical nodal involvement such as some large T2 tumors or rapidly growing tumors, on the other hand when there was no evident risk of nodal metastasis neck dissection was not performed and nodes status was determined depending on adjunctive findings obtained during the follow-up procedures.

According to the size of tumor there were 21 patients with T1 tumor (52.5%), and 19 patients with T2 tumor (48.5%). According to the histological grade there were 27 cases of grade I tumors (71%) and 13 cases of grade II tumors (29%).

Regional lymph node metastasis was discovered in 14 patients of our complete sample (35%), 9 cases (22.5 %) of them were discovered histologically after elective neck dissection, and 5 cases (12.5%) were discovered later during the follow-up period.

Tumor Thickness in our whole sample ranged between 1 and 14 mm (mean: 6.05 mm), with a range of (2- 14 mm) in the positive lymph nodal group (mean: 8.07 mm), and a range of (1 - 11 mm) in the negative lymph nodal group (mean: 4.96 mm).

The positive lymph nodal group was characterized by higher values of tumor thickness compared with the negative nodal group and the difference in TT values was statistically significant (t-test, p value= 0.006). These results demonstrated that increased tumor thickness values were associated with more incidence of nodal involvement in our OTSCC sample.

Table (1) Nodal status and patients' statistics are illustrated in table 1.

Eleven patients were included in Group 1 of thickness (<3mm),

twelve patients in group 2 (3-6mm), and seventeen patients in group 3 (>6mm). Two cases of the 11 patients included in group 1 had regional node metastasis (18.18%), 4 cases in group 2 (33.33%), and 8 cases in group 3 (47.05%). There was a progressive increase in the incidence of regional nodal metastasis from the thinner tumors' groups to the thicker tumors' groups which was an expected result because of the aforementioned statistical relation between regional nodal involvement and the increased tumor thickness values.

Table (2) Tumor thickness groups and the related nodal metastasis incidence are illustrated in table 2.

Discussion

TNM tumor classification system depends on tumor size in determining disease stage and expected prognosis and in establishing the standard treatment plan. [8, 9] Many recent studies have demonstrated the presence of other prognostic factors that influence tumors' progress in general and oral squamous cell carcinoma in particular such as tumor thickness or tumor depth of invasion, tumor's histological grade, perineural invasion, and many other risk factors. [21-33]

Tumor thickness is considered an important risk factor for regional lymph node involvement. [21-24] It may be of superior influence when compared with tumor maximum dimension as many recent trials have concluded. [10, 23, 30]

We evaluated in our study the role of tumor thickness (TT) of oral tongue SCC in the incidence of late regional lymph node metastasis by analyzing TT values in both studied nodal groups (positive lymph node metastasis group and negative lymph node metastasis group) and then statistically comparing the tumor thickness values in our two nodal groups.

Also, we analyzed the incidence of regional nodal metastasis in three different ranges of tumor thickness in order to detect the thickness range that is associated with higher probability to develop regional lymph node metastasis.

In order to lessen the misdirection in our study we exclude all cases that is characterized with high or low tendency for nodal involvement such T3, T4 tumors which were excluded due to the high probability of these tumors to develop lymph node metas-

Table 1. Nodal status and statistics related to patients' number and mean tumor thickness.

Node's status	Number	Percentage (%)	Mean thickness (mm)
N+	14	35	8.07
N0	26	65	4.96
Total	40	100	6.05

Table 2. Tumor thickness groups and related nodal metastasis incidence.

Tumor thickness (mm)	Number	N+	N0	Percentage (%)
0-2.9	11	2	9	18.18
3-5.9	12	4	8	33.33
≥6	17	8	9	47.05

tasis, also we exclude the tumors of histological grade III, tumors with histologically confirmed perineural or Angio vascular invasion and the recurrent tumors for the same aforementioned reason.

On the other hand, all cases that were diagnosed as carcinoma in situ or exophytic type cancers were also excluded because of the low incidence of regional nodes involvement in these kinds of tumors.

Ultimately our study sample included 40 patients whose neck were negative in clinical and radiological examination. Tumor thickness in the positive nodal metastasis group ranged between 2 and 14 mm with a mean thickness of 8.96 mm, and between 1 mm and 11 mm in the negative nodal metastasis group with a mean thickness of 4.96 mm. TT values were larger in the positive nodal group with a significant difference as resulted in statistical study (p value=0.006).

These results conducted with our attempt to exclude the known risk factors that may affect regional nodal metastasis make us conclude that thicker tongue tumors have the tendency to develop regional nodal metastasis more than thinner tumors.

Regional nodal metastasis occurred in 14 patients of our whole sample (35%). This percentage varies in previous studies on OTSCC patients for many reasons relating to the inclusion criteria of each study and the range of thickness values for their included tumors. In a review of the incidence of late cervical nodal metastasis in these studies, we find that the rate was 14% in the study of Kurokawa, 28.88% in Sparano study, 47.7% in Asakage study, 19.3% in Shin study, and 43% in Yuen study. [31-35]

In our study there was a progressive increase in the rate of late regional nodal involvement from groups of lesser thickness to groups of larger thickness. In the group of tumor thickness <3mm there was 18.18% of regional lymph node metastasis, with this percentage increased to 33.33% in the group of thickness 3-6mm and 47.05% in the group >6mm thick. This increase in the nodal metastasis incidence was expected because of the aforementioned statistical relation between regional nodal metastasis incidence and the increased tumor thickness values in our study sample.

Yuen et al had recorded 8% of regional nodal metastasis for tumors' thickness less than 3mm, 44.6% for tumors of thickness between 3 and 9mm, and 53% for tumors' thickness >9mm. [35] The thickness range between 3 and 9mm was here large and needed an equal distributions of thickness values to reach the real percentage of metastasis incidence related to this group, because this percentage is affected directly by the prevalent values of thickness whether it is high or low values, in other words if high thickness values are the dominant there will be a bias in results to more incidence of regional node metastasis in this group, and if low thickness values are the dominant there will be a bias in results to less incidence of regional node metastasis in this group.

Shin et al had also studied the influence of tumor's deep of invasion in OTSCC patients and had recorded 7.4% of regional nodal metastasis for tumors DOI of less than 3mm, and 23.2% for tumors DOI of more than 3mm, [34] also here the group (>3mm) was of large range of DOI values and again the nodal metastasis

percentage will be affected by the prevalent DOI values of the group whether it is high or low values.

There was an agreement in previous studies that when occult nodal involvement exceeds the percentage 20%, then neck therapy with elective neck dissection or irradiation is indicated. [10, 20, 21] Concerning to tumors of thickness <3mm we have 18.18% nodal involvement, this rate exceeded the critical value of 20% in the thickness group of 3-6mm and the group >6mm with nodal involvement rate 33.33% and 47.05% respectively, and according to these results elective neck dissection or irradiation should be considered for tumors of more than 3 mm thick.

Conclusion

Tumor Thickness is a predictor for regional lymph node metastasis in oral tongue SCC patients. There was a significant incidence of nodal metastasis in OTSCC tumors of more than 3mm thick in comparison with tumors of less 3mm thick.

We recommend –within limits of this study- prophylactic neck dissection or prophylactic neck irradiation and close follow-up procedures for patients with more than 3mm thick oral tongue SCC tumors.

Acknowledgment

Damascus University funded this study

References

- Warnakulasuriya S. Global Epidemiology of Oral and Oropharyngeal Cancer. *Oral Oncol.* 2009 Apr;45(4):309-316. Pubmed PMID: 18804401.
- Moore SR, Johnson NW, Pierce AM, Wilson DE. The epidemiology of tongue cancer: a review of global incidence. *Oral diseases.* 2000 Mar;6(2):75-84. Pubmed PMID: 10702783.
- de Araújo Júnior RF, Barboza CA, Clebis NK, de Moura SA, Costa AD. Prognostic significance of the anatomical location and TNM clinical classification in oral squamous cell carcinoma. *Medicina oral, patologia oral y cirugía bucal.* Ed. inglesa. 2008;13(6):3.
- Weiss MH, Harrington LB, Isaacs RS. Use of decision analysis in planning a management strategy for the stage NO neck. *Archives of Otolaryngology-Head & Neck Surgery.* 1994 Jul 1;120(7):699-702.
- Kurokawa H, Yamashita Y, Murata T, Tokudome S, Miura K, Yoshikawa T, et al. Clinico-pathological Evaluation of Prognostic Factors of Oral Squamous Cell Carcinoma Patients with Stage I and II. *The Journal of the Kyushu Dental Society.* 1998 Aug 25;52(4):399-404.
- Abu-Ghanem S, Yehuda M, Carmel NN, Leshno M, Abergel A, Gutfeld O, Fliss DM. 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 Otolaryngology-Head & Neck Surgery.* 2016 Sep 1;142(9):857-65.
- Listl S, Jansen L, Stenzinger A, Freier K, Emrich K, Holleczeck B, Katalinic A, Gondos A, Brenner H, GEKID Cancer Survival Working Group. Survival of patients with oral cavity cancer in Germany. *PLoS one.* 2013 Jan 18;8(1):e53415.
- Pollaers K, Hinton-Bayre A, Friedland PL, Farah CS. AJCC 8th Edition oral cavity squamous cell carcinoma staging-Is it an improvement on the AJCC 7th Edition?. *Oral oncology.* 2018 Jul 1;82:23-8.
- Crescenzi D, Laus M, Radici M, Croce A. TNM classification of the oral cavity in oral tongue carcinoma: a suggested modification. *Otolaryngologia polska= The Polish otolaryngology.* 2015 Jan 1;69(4):18-27. Pubmed PMID: 26388356.
- Wang K, Veivers D. Tumour thickness as a determinant of nodal metastasis in oral tongue carcinoma. *ANZ journal of surgery.* 2017 Sep;87(9):720-4.
- O-charoenrat P, Pillai G, Patel S, Fisher C, Archer D, Eccles S, Rhys-Evans P. Tumour thickness predicts cervical nodal metastases and survival in early oral tongue cancer. *Oral oncology.* 2003 Jun 1;39(4):386-90.
- Po Wing Yuen A, Lam KY, Lam LK, Ho CM, Wong A, Chow TL, et al. Prognostic factors of clinically stage I and II oral tongue carcinoma—a com-

- parative study of stage, thickness, shape, growth pattern, invasive front malignancy grading, Martinez-Gimeno score, and pathologic features. *Head & Neck: Journal for the Sciences and Specialties of the Head and Neck*. 2002 Jun;24(6):513-20. Pubmed PMID: 12112547.
- [13]. Spiro RH, Huvos AG, Wong GY, Spiro JD, Gnecco CA, Strong EW. Predictive value of tumor thickness in squamous carcinoma confined to the tongue and floor of the mouth. *The American journal of surgery*. 1986 Oct 1;152(4):345-50. Pubmed PMID: 3766861.
- [14]. Rasgon BM, Cruz RM, Hilsinger RL, Sawicki JE. Relation of lymph node metastasis to histopathologic appearance in oral cavity and oropharyngeal carcinoma: a case series and literature review. *Laryngoscope* 1989; 99: 1103–10. Pubmed PMID: 2682099.
- [15]. Shingaki S, Suzuki I, Nakajima T, Kawasaki T. Evaluation of histopathologic parameters in predicting cervical lymph node metastasis of oral and oropharyngeal carcinomas. *Oral Surg. Oral Med. Oral Pathol*. 1988; 66: 683–8. Pubmed PMID: 3205557.
- [16]. Tai SK, Li WY, Yang MH, Chu PY, Wang YF. Perineural invasion in T1 oral squamous cell carcinoma indicates the need for aggressive elective neck dissection. *Am J Surg Pathol* 2013;37(8):1164–72 Pubmed PMID: 23681077.
- [17]. Michikawa C, Uzawa N, Kayamori K, Sonoda I, Ohyama Y, Okada N, et al. Clinical significance of lymphatic and blood vessel invasion in oral tongue squamous cell carcinomas. *Oral Oncol* 2012;48(4):320–4. Pubmed PMID: 22178206.
- [18]. Byers RM, El-Naggar AK, Lee YY, Rao B, Fornage B, Terry NH, et al. Can we detect or predict the presence of occult nodal metastases in patients with squamous carcinoma of the oral tongue? *Head Neck* 1998;20(2):138–44. Pubmed PMID: 9484945.
- [19]. Bundgaard T, Bentzen SM, Wildt J, Sørensen FB, Søgaard H, Nielsen JE. Histopathologic, stereologic, epidemiologic, and clinical parameters in the prognostic evaluation of squamous cell carcinoma of the oral cavity. *Head & Neck: Journal for the Sciences and Specialties of the Head and Neck*. 1996 Mar;18(2):142-52.
- [20]. Balasubramanian D, Ebrahimi A, Gupta R, Gao K, Elliott M, Palme CE, et al. Tumour thickness as a predictor of nodal metastases in oral cancer: comparison between tongue and floor of mouth subsites. *Oral oncology*. 2014 Dec 1;50(12):1165-8.
- [21]. O'Brien CJ, Lauer CS, Fredricks S, Clifford AR, McNeil EB, Bagia JS, et al. Tumor thickness influences prognosis of T1 and T2 oral cavity cancer—but what thickness?. *Head & Neck: Journal for the Sciences and Specialties of the Head and Neck*. 2003 Nov;25(11):937-45. Pubmed PMID: 14603454.
- [22]. O-charoenrat P, Pillai G, Patel S, Fisher C, Archer D, Eccles S, et al. Tumour thickness predicts cervical nodal metastases and survival in early oral tongue cancer. *Oral oncology*. 2003 Jun 1;39(4):386-90. Pubmed PMID: 12676259.
- [23]. Kane SV, Gupta M, Kakade AC, D'Cruz A. Depth of invasion is the most significant histological predictor of subclinical cervical lymph node metastasis in early squamous carcinomas of the oral cavity. *European Journal of Surgical Oncology (EJSO)*. 2006 Sep 1;32(7):795-803.
- [24]. Alkureishi LW, Ross GL, Shoaib T. Does tumor depth affect nodal upstaging in squamous cell carcinoma of the head and neck? *Laryngoscope*. 2008 Apr;118(4):629-34.
- [25]. Woolgar JA, Scott J. Prediction of cervical lymph node metastasis in squamous cell carcinoma of the tongue/floor of mouth. *Head & neck*. 1995 Nov;17(6):463-72.
- [26]. Moore C, Kuhns JG, Greenberg RA. Thickness as prognostic aid in upper aerodigestive tract cancer. *Arch Surg* 1986; 121:1410–1414. Pubmed PMID: 3789911.
- [27]. Yilmaz T, Hosal S, Gedikoglu G, Turan E, Ayas K. Prognostic significance of depth of invasion in cancer of the larynx. *Laryngoscope* 1998;108:764–768. Pubmed PMID: 9591560.
- [28]. Inoue T. Prognostic significance of depth of invasion relating to nodal metastases, parametrial extension, and cell types. *Cancer* 1984;54:3035–3042. Pubmed PMID: 6498777.
- [29]. Mannelli G, Comini LV, Piazza C. Surgical margins in oral squamous cell cancer: intraoperative evaluation and prognostic impact. *Current opinion in otolaryngology & head and neck surgery*. 2019 Apr 1;27(2):98-103. Pubmed PMID: 30844923 .
- [30]. S V Kane et al. Depth of invasion is the most significant histological predictor of subclinical cervical lymph node metastasis in early squamous carcinomas of the oral cavity. *Eur J Surg Oncol*. 2006 Sep. Pubmed PMID:16777368.
- [31]. Kurokawa H, Yamashita Y, Takeda S, Zhang M, Fukuyama H, Takahashi T. Risk factors for late cervical lymph node metastases in patients with stage I or II carcinoma of the tongue. *Head & neck*. 2002 Aug;24(8):731-6.
- [32]. Sparano A, Weinstein G, Chalian A, Yodul M, Weber R. Multivariate predictors of occult neck metastasis in early oral tongue cancer. *Otolaryngology—Head and Neck Surgery*. 2004 Oct;131(4):472-6.
- [33]. Asakage T, Yokose T, Mukai K, Tsugane S, Tsubono Y, Asai M, Ebihara S. Tumor thickness predicts cervical metastasis in patients with stage I/II carcinoma of the tongue. *Cancer: Interdisciplinary International Journal of the American Cancer Society*. 1998 Apr 15;82(8):1443-8. Pubmed PMID: 9554518.
- [34]. Shin JH, Yoon HJ, Kim SM, Lee JH, Myoung H. Analyzing the factors that influence occult metastasis in oral tongue cancer. *Journal of the Korean Association of Oral and Maxillofacial Surgeons*. 2020 Apr 30;46(2):99. Pubmed PMID: 32364349 .
- [35]. Po Wing Yuen A, Lam KY, Lam LK, Ho CM, Wong A, Chow TL, 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: Journal for the Sciences and Specialties of the Head and Neck*. 2002 Jun;24(6):513-20.