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Controversies in the treatment of early-stage oral squamous cell carcinoma

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ABSTRACT

The treatment of early-stage oral squamous cell carcinoma (OSCC) is still a controversial issue. Thanks to the 8th edition of TNM by AJCC there is a better distinction between the stages of OSCC. However, Stages I and II still share the same treatment protocol, even if the prognosis is radically different. A retrospective study has been conducted including 70 previously untreated patients with Stage I or II OSCC, treated with tumorectomy and selective neck dissection. The study focuses on the link between pT1/2 and various other factors, particularly histological grading, vascular and perineural invasion, local and cervical recurrence, surgical margins and overall survival. These data reveal significant differences between pT1 and pT2 in histological grade, perineural invasion, cervical recurrence, surgical margins, and overall survival, emphasizing the necessity of different treatment protocols for T1 and T2 OSCC. Distinct strategies should be proposed to treat Stage I and II OSCC, with Stage II patients possibly benefitting from more aggressive treatments: following these data, a wait-and-see strategy should only be considered in Stage I, while certain treatments at the cervical level — such as prophylactic neck dissection and sentinel node biopsy — should always be considered for Stage II tumors.

Introduction

Squamous cell carcinoma of the oral cavity represents a serious disease with a possible devastating impact on patients' overall survival and quality of life.[1] Despite advancements in treatment strategies and a better understanding of the disease, overall survival has not yet improved in recent years[2] According to Warnakulasuriya, tongue cancer is the most frequent intra-oral cancer among the US and European population[1] Currently, several studies are being carried out to better understand the impact of patients' factors (e.g. age and gender) or clinical and pathological tumor factors. Further research is still needed to clarify the role of specific factors on survival time.[3] The TNM system represents an important instrument to help clinicians choose appropriate treatment and to standardize

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tumors' categories. Specifically, it is based on classifying the disease through the analysis of its dimension (T), lymph nodes involvement (N) and metastasis (M). The main changes in the 8th edition of TNM classification are the inclusion of depth of invasion (DOI) and extracapsular spreading (ECS) as parameters to state T and N, respectively. In this sense, some authors noted that the modifications of the 8th edition caused an upstaging compared to the 7th edition. In fact, Lee et al. noted an upstaging of 12.4 % in pT stage and 13,3 % for pN stage, while Almangush et. al noted an upstaging from T1 and T2 and from T2 and T3 when DOI was incorporated in the classification system.[4,5]

However, TNM staging is not enough to predict prognosis and to define treatment for all cases and other factors such as loco-regional recurrence, perineural invasion, depth of invasion, vascular invasion, surgical margins, histological grading, genetic alterations and molecular biomarkers need to be considered. The inclusion of other prognostic factors could be important to improve overall survival and to reduce the treatment morbidity. For instance, several recent studies are focusing on tumor grading as an important prognostic factor to guide the treatment strategy especially at early stages (pT1-2 N0). Early stage treatment of squamous cell carcinoma of the oral cavity usually results in good outcomes. Nevertheless, the reason why some patients present an extremely poor evolution in terms of overall survival is unknown. The main aim of the present report is to analyze the clinical and histological differences between the two groups of tumors considered as early stage (pT1N0 vs pT2N0) and to try to understand if a different treatment strategy according to patient T-stage could be useful to improve overall survival.

Material and Methods

Between 2014 and 2018, 70 previously untreated patients with pT1N0 or pT2N0 squamous cell carcinoma of the oral cavity were diagnosed and treated with at least a tumorectomy and prophylactic neck dissection. Criteria for performing neck dissection were tumor site, suspect of tumor thickness $>$ 0.5 cm (or $>$ 0.3 cm in case of tongue cancer) and clinical or radiological suspect of cervical involvement. The neck dissections included Levels I-III in patients with clinically negative neck. However, the neck was recorded as clinically positive (cN+) in cases where there was suspicion of any clinical or radiological node involvement. Specifically, the clinical palpation of hard and immobile nodes and the radiological evidence (CT scan) of nodes with a 10-15 mm in maximum transverse diameter in levels I and II or 10 mm for the rest of levels, rounded shape, and focal necrosis were the criteria used to classify the patients as clinically N+.[6] In these cases, comprehensive prophylactic neck dissection was carried out at Levels I-V. Careful clinical exploration and a CT scan of the cervicofacial area were performed in all patients before surgery. The clinical stage of the primary tumor was determined by using the most recent recommendations of the UICC at the time of the diagnosis.[7] However, all the cases were re-staged by using the recommendations of the 8th edition of the AJCC/UICC TNM classification to perform the data analysis reported in this study.[8] Several histological factors such as T-stage, N stage, surgical margins, tumor grade, perineural invasion, vascular invasion, and local and cervical recurrence were analyzed and correlated to overall survival. The degree of tumor differentiation was analyzed for all cases, and the patients were accordingly divided into two groups: patients with well-differentiated tumors (Group 1) and those with moderately and poorly differentiated tumors (Group 2). Surgical margins were defined as clear ($>$5 mm), close (between 2 and 5 mm), and positive ($<$2 mm).[9] Correlation tests and Chi-square tests were carried out in order to analyze the relation between tumor stage and other variables, while Kaplan-Meier analysis was performed to analyze the overall survival. Statistical analysis was carried out using SPSS 23v.

Results

Our study included 70 patients with a postoperative diagnosis of early-stage squamous cell carcinoma. Patients were divided in 2 groups: Group 1 included patients with pT1 (n=34; 48.6% of our sample) while Group 2 included patients with pT2 tumors (n= 36; 51.4%). (Table 1 and Table 2).

Histological grade

A statistically significant difference was found when comparing histological grade with pT-stage ($p<0.05$). Specifically, 73.5% of patients in Group 1 (n=25, 25 of 34 patients) and 38.9% of patients in Group 2 (n=14, 14 of 36 patients) showed well-differentiated tumors. On the other hand, 26.5% of Group 1 (n=9, 9 of 34 patients) and 61.1 % of Group 2 (n=22, 22 of 36 patients) presented moderately or poorly differentiated tumors (Fig. 1).

Perineural and vascular invasion

No significant correlation was found between vascular invasion and pT stage ($p>0.05$). However, a significant correlation emerged

Table 1
Intraoral distribution of the tumours.

	Floor of mouth	Palate	Gingiva	Oropharynx	Tongue	Retromolar trigone	Buccal mucosa	Total
pT1	3	0	2	0	12	14	3	34
pT2	11	1	1	2	16	5	0	36
Total	14	1	3	2	28	19	3	70

Table 2
Descriptive characteristics of the cases.

Variables	Total = N	Total = %
pT stage		
pT1	34	48,6 %
pT2	36	51,4 %
Histological grading		
Well differentiated	39	55,7 %
Moderately or poorly differentiated	31	44,3 %
Depth of invasion (DOI)		
1-5 mm	40	57,1 %
5-10 mm	17	24,3 %
Perineural invasion		
Yes	18	25,7 %
No	52	74,3 %
Vascular invasion		
Yes	2	2,9 %
No	68	97,1 %
Local recurrence		
Yes	10	14,5 %
No	59	85,5 %
Cervical recurrence		
Yes	11	15,7 %
No	59	84,3 %
Surgical margins		
Clear (>5 mm)	44	62,9 %
Close (2-5 mm)	11	15,7 %
Positive (0-2 mm)	15	21,4 %

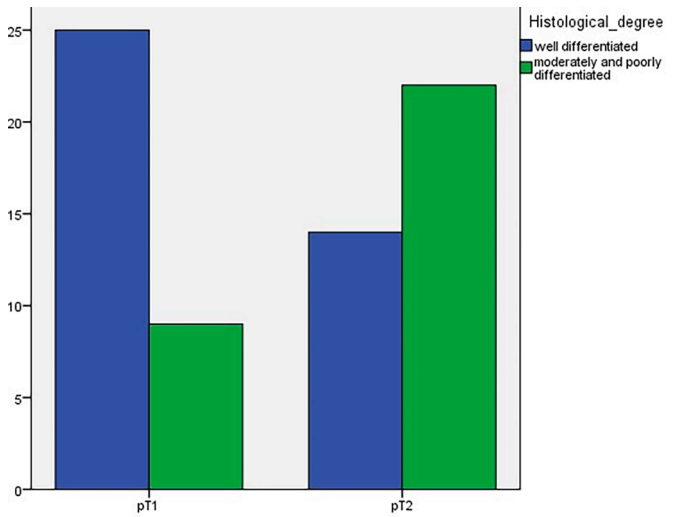

Fig. 1. Relationship between pT stage and histological degree.

between T-stage and perineural invasion ($p<0.01$). In fact, only one patient in Group 1 showed perineural invasion (2.9%, n=1, 1 of 34 patients), while 47.2 % of the patients in Group 2 showed perineural invasion (n=17, 17 of 36 patients) after histological examination (Fig. 2).

Local and cervical recurrence

No statistically significant difference was found in terms of local recurrence. In fact, local recurrence rate was 14.7% in Group 1 (n=5; 5 of 34 patients) vs 13.8% in Group 2 (n=5; 5 of 36 patients) ($p>0.05$). However, a significant difference was identified in terms of cervical relapses ($p<0.05$). Specifically, only 2 patients of Group 1 showed a cervical recurrence during follow-up (5.9%, n=2, 2 of 34 patients). In contrast, 9 patients in Group 2 showed one (23%, n=9; 9 of 36 patients). (Fig. 3).

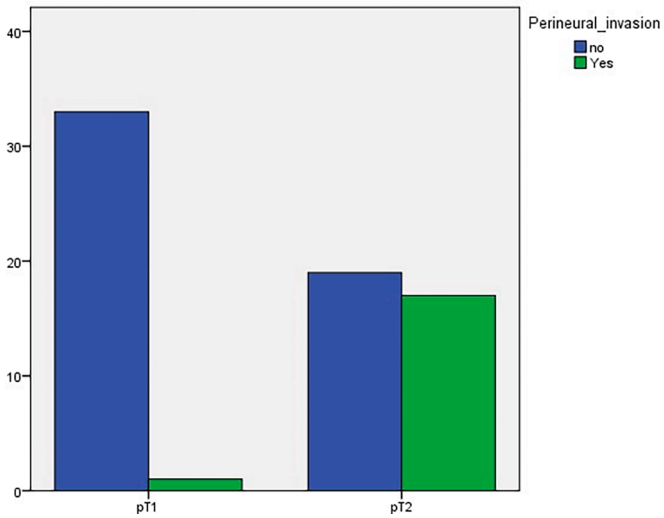

Fig. 2. Relationship between pT stage and perineural invasion.

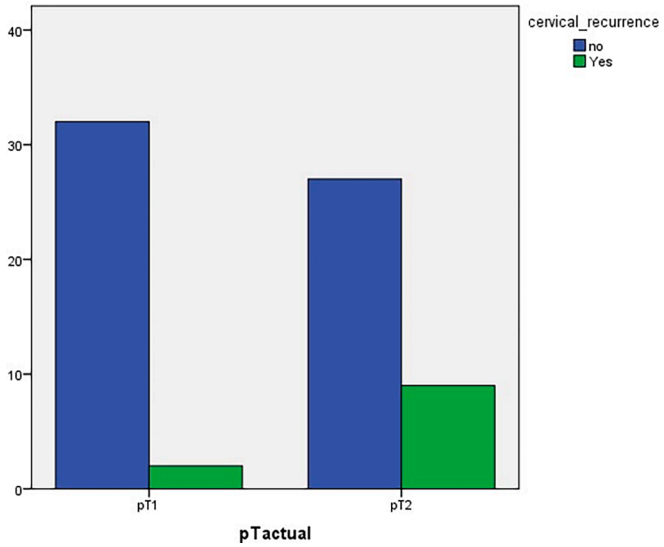

Fig. 3. Relationship between pT stage and cervical recurrence.

Locoregional recurrence

With locoregional recurrence our study refers to the presence of an extent recurrence originating in the oral cavity and involving simultaneously the cervical region. Locoregional recurrence was 0% in Group 1 (0 of 34 patients) and 13.9% in Group 2 (n=5; 5 of 36 patients). This could be related to the higher rate of close and involved surgical margins in the group of patients with pT2 tumors. It is important to note that all patients that showed locoregional recurrence died during the follow up.

Table 3
Surgical margins

	Surgical margins			
	0-2 mm	2-5 mm	>5 mm	Total
pT1	3	3	28	34
pT2	12	8	16	36
Total	15	11	44	70

Surgical margins

A statistically significant difference was also found between pT stage and surgical margins ($p< 0,01$). Only 3 of the 34 patients in Group 1 showed positive margins (8.8%), while involved margin was observed in 12 patients of 36 in Group 2 (33.3%). A total of 11 patients had close margins (15.7%, 11 of 70 patients), 3 of them belonging to Group 1 and 8 to Group 2 (respectively 8.8% vs. 22.2%). Most of the patients showed clear margins (62.8%, 44 of 70 patients): 28 in Group 1 (82.4%, 28 of 34 patients) and 16 in Group 2 (44.4%, 16 of 36 patients). Distribution of surgical margins among Group 1 and 2 are summarized in Table 3.

Overall survival

The analysis of survival rate showed a statistically significant difference between the two groups. In fact, overall survival was 97% in group 1 and 72.2% in group 2 ($p<0.05$). (Fig. 4)

Influence of prognostic factors in pT1 group

Interesting findings come out from the analysis of the impact of each prognostic factor in the group of pT1 patients. In fact, this analysis would show that only the pathological stage would have an impact on the overall survival. The entirety of the other prognostic factors analyzed in our sample would not influence the mortality of patients with OSCC. Unfortunately, the entity of the sample in our study does not achieve statistically significant results ($p>0.05$). The findings are resumed in Table 4. The influence of prognostic factors in pT2 group is showed in Table 5.

Discussion

The treatment of early stage OSCC is still controversial. Even in early stages there is a certain risk of loco-regional recurrence, occult cervical involvement and even of distant metastasis. Our data show a significant difference in OS between T1 and T2 (97% vs 72.2%). Our results are comparable with other studies in the field.[10,11] Analyzing our data indicates that different factors are related to a different behavior and prognosis between T1 and T2, in particular: histological grade, perineural invasion, cervical recurrence, surgical margins and overall survival. The importance of this analysis lies in the fact that pT1N0 and pT2N0 presented the same treatment protocols even if they are classified as two different stages. In fact, pT1N0 is classified as stage 1 and pT2N0 is classified as stage 2. The main question of our study is if these two groups of tumors would benefit from different treatment strategies. Our data showed that pT2N0 usually presents worse outcomes when compared to pT1N0. This is probably related to the presence of poor prognostic factors. Histological grade takes on more importance as a prognostic factor in OSCC. Kademani et al. highlighted the importance of tumor grade as a prognostic factor.[12] However, the 8th edition of the AJCC/UICC TNM classification attributed relatively little importance to the degree of tumor differentiation.[13] Hence, there are no alternative treatment protocols available for patients with moderately or poorly differentiated OSCC. Our data showed a significant relation between histological grade and T staging, suggesting a decrease of tumor differentiation following its spread and growth. Our results are in line with those of other authors, who found out a strong relation between histological grade and poor prognostic factors such as node involvement, recurrence rate, perineural invasion, vascular invasion, and surgical margins.[13]

Perineural invasion (PNI) is also considered an important prognostic factor. Subramaniam et al. analyzed 296 patients with early stages OSCC (classified by AJCC 8th edition) and found out that a combination of moderately/poorly differentiation and perineural invasion were associated with worse loco-regional control compared to either factor individually and that perineural invasion affected loco-regional control both in stage I and II.[14] In this sense, our data showed a strong association between both PNI, tumor differentiation and overall survival. Moreover, our data showed that cervical recurrence is much more frequent in stage 2 than in stage 1.

The main approaches for management of clinically negative neck (cN0) with T1-2 tumors are prophylactic neck dissection, sentinel node biopsy and a wait-and-see strategy (W&S). Neck dissection could not always be recommended because of its morbidity, while a W&S approach could increase the risk of delayed neck metastasis. According to Abu-Ghanem et al., the rate of occult neck metastasis in cT1- 2N0 oral tongue SCC ranges from 8.2% to 46.3%, with an average of 25.9%.[15] On the other hand, neck dissection is associated with some complications, such as cosmetic defects due to scarring, accessory nerve paralysis, stiffness of shoulder and neck. For these reasons, surgeons adopt different treatment strategies regarding neck management: based on the prospective, randomized, controlled trial of D'Cruz et al., some surgeons offer prophylactic neck dissection to all T1 and T2 OSCC patients, while others utilize DOI thresholds to guide the treatment.[16] Moreover, some surgeons consider the elective neck dissection if the neck must be accessed for microvascular reconstruction. Our group recommend elective neck dissection in patients with a suspected tumor thickness $>$ 0.5 cm (or $>$ 0.3 cm in tongue cancer).[17,18] Since patients with pT2N0 tumors sustained more frequent cervical recurrences than pT1N0, a distinct or more aggressive treatment paradigm for pT2N0 lesions may be warranted. Cervical recurrence is the most important prognostic factor for overall survival, and this might explain the difference in survival observed between the two groups. Due to these results, a more aggressive treatment of the neck might prove useful in stage 2 OSCC. In our opinion, a wait-and-see strategy could be considered only in stage 1 while some type of treatment at the cervical level such as prophylactic neck dissection or sentinel node biopsy need to be considered for stage 2 tumors. In this sense, D'Cruz et al. suggested that elective neck dissection could be important for improving overall survival among patients with early stage OSCC.[16] The impact of surgical margin should also be deeply analyzed. Specifically, surgical margin is the only factor potentially controlled by the surgeons. pT2 tumors usually show greater depth of invasion compared to pT1. The depth margin was the most frequently involved after postoperative histological analysis in our study. This

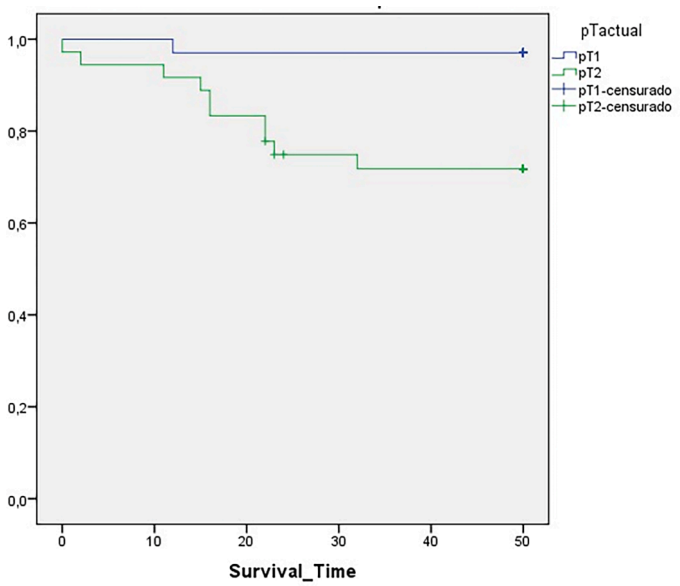

Fig. 4. Kaplan-Meier curve describing the difference in survival between Groups 1 and 2.

Table 4
Influence of prognostic factors in pT1 group.

Prognostic Factor	Alive	Death	p
Histological degree			p=0.265
-Well differentiated	25/25 (100%)	0	
-Moderately and poor differentiated	8/9 (88.9%)	1/9 (11.1%)	
Perineural invasion			p=0.971
No	32/33 (97%)	1/33 (3%)	
Yes	1/1 (100%)	0	
Vascular invasion			p=0.971
No	32/33 (97%)	1/33 (3%)	
Yes	1/1 (100%)	0	
Local Recurrence			p=0.853
No	28/29 (96.6%)	1/29 (3.4%)	
Yes	5/5 (100%)	0	
Cervical recurrence			p=0.941
No	31/32 (96.9%)	1/32 (3.1%)	
Yes	2/2 (100%)	0	
Surgical Margins			p=0.895
Clear	27/28 (96.4%)	1/28 (3.6%)	
Close	3/3 (100%)	0	
Positive	3/3 (100%)	0	

is comparable with other studies in the field. It is well established that surgeons should try to leave at least a 1 cm macroscopic margin to obtain microscopic margins greater than 0.5 cm. Considering that surgical margin is the only factor potentially controlled by the surgeon and that the presence of positive margin is directly proportional to the depth of invasion it is logical to ask if the obtention of a greater macroscopic margin during surgery could improve the outcomes in stage 2 patients. In our sample, 33.3% of patients of group 2 showed involved margin after surgery. In this regard, other authors noted that even early stage tumours could be associated with high rate of close or involved margins; in our study this may be due to the high number of T2 tumours involving floor of the mouth, where the obtention of free margins could be more difficult with respect of other oral sites.[19,20,21] Even if all these patients were treated with re-operation to widen the margin or with adjuvant treatment (radiotherapy or radiotherapy + chemotherapy when indicated), when re-operation was impossible or not indicated, overall survival remained poor in this group. In this sense, several studies showed that re-operation is not more effective than adjuvant treatment to improve overall survival in the presence of involved margin.

It is not clear if the obtention of greater surgical margins could be helpful in improving overall survival in patients with early stage OSCC. In this sense, further studies evaluating the effect of greater surgical margins on overall survival could help to understand the correct management of this group of patients.[22,23]

Table 5
Influence of prognostic factors in pT2 group.

Prognostic Factor	Alive	Death	p
Histological degree			p=0.144
-Well differentiated	12/14 (85.7%)	2/14 (14.3%)	
-Moderately and poor differentiated	14/22 (63.6%)	8/22 (36.4%)	
Perineural invasion			p=0.281
No	15/19 (78.9%)	4/19 (21.1%)	
Yes	11/17 (64.7%)	6/17 (35.3%)	
Vascular invasion			p=0.722
No	25/35 (71.4%)	1/1 (100%)	
Yes	10/35 (28.6%)	0	
Local Recurrence			p=0.429
No	23/31 (74.2%)	8/31 (25.8%)	
Yes	3/5 (60%)	2/5 (40%)	
Cervical recurrence			p=0.001
No	24/27 (88.9%)	3/27 (11.1%)	
Yes	2/9 (22.2%)	7/9 (77.8%)	
Surgical Margins			p=0.09
Clear	11/16 (68.7%)	5/16 (31.3%)	
Close	4/8 (50%)	4/8 (50%)	
Positive	11/12 (91.6%)	1/12 (8.4%)	

Conclusion

In our opinion, different protocol strategies would be necessary to treat stage 1 and stage 2 oral squamous cell carcinoma. Stage 2 might benefit from a more aggressive treatment. In our opinion, a wait-and-see strategy could be considered only in stage 1 while some type of treatment at the cervical level such as prophylactic neck dissection or sentinel node biopsy need to be considered for stage 2 tumors. We are aware that this study presents some limitations. For instance, this is a retrospective study and the sample is small. However, we believe that it is important to start considering that stage 1 and stage 2 oral squamous cell carcinoma need to be treated with different protocol strategies. This could notably improve the prognosis of patients with stage 2 tumors.

CRediT authorship contribution statement

Leonardo Ferrari: Methodology, Data curation, Investigation, Writing – original draft, Visualization. **Paolo Cariati:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization. **Imanol Zubiate:** Formal analysis, Writing – review & editing. **Ángel Martínez-Sahuquillo Rico:** Software, Validation, Writing – review & editing. **Susana Arroyo Rodriguez:** Formal analysis, Supervision, Project administration. **Rosa Maria Pulgar Encinas:** Formal analysis, Supervision, Project administration. **Silvano Ferrari:** Formal analysis, Validation, Supervision, Project administration. **Ildefonso Martínez Lara:** Writing – review & editing, Formal analysis, Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

1. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. *Oral Oncol*. 2009;45(4–5):309–316.
2. Rivera C. Essentials of oral cancer. *Int J Clin Exp Pathol*. 2015;8(9):11884–11894.
3. Kelly A, Ferreira A, Henrique S, de Carvalho G, Granville-garcia AF. *Survival and prognostic factors in patients with oral squamous cell carcinoma*. 2021;26(3).
4. Lee NCJ, Eskander A, Park HS, Mehra S, Burtness BA, Husain Z. Pathologic staging changes in oral cavity squamous cell carcinoma: Stage migration and implications for adjuvant treatment. *Cancer*. 2019 Sep 1;125(17):2975–2983.
5. Almangush A, Mäkitie AA, Mäkinen LK, Kauppila JH, Pukkila M, Hagström J, et al. Small oral tongue cancers (≤ 4 cm in diameter) with clinically negative neck: from the 7th to the 8th edition of the American Joint Committee on Cancer. *Virchows Archiv*. 2018 Oct 1;473(4):481–487.
6. Som PM, Curtin HD, Mancuso AA. An Imaging-Based Classification for the Cervical Nodes Designed as an Adjunct to Recent Clinically Based Nodal Classifications. *Arch Otolaryngol Head Neck Surg*. 1999 Apr 1;125(4):388.
7. Sobin LH, Fleming ID. *TNM classification of malignant tumors* (1997). In: *Cancer*. fifth edition 80. 1997:1803–1804. Nov 1.
8. Huang SH, O'Sullivan B. TNM Classification for Head and Neck Cancer. *Curr Treat Options Oncol*. 2017 Jul 29;18(7):40.
9. Kain JJ, Birkeland AC, Udayakumar N, Morlandt AB, Stevens TM, Carroll WR, et al. Surgical margins in oral cavity squamous cell carcinoma: Current practices and future directions. *Laryngoscope*. 2020 Jan 26;130(1):128–138.

10. Vuity D, McMahon J, Takhiuddin S, Slinger C, McLellan D, Wales C, et al. Is the 8th edition of the Union for International Cancer Control staging of oral cancer good enough? *British Journal of Oral and Maxillofacial Surgery*. 2018 May 1;56(4):272–277.
11. Murthy S, Low TH (Hubert), Subramaniam N, Balasubramanian D, Sivakumaran V, Anand A, et al. Validation of the eighth edition AJCC staging system in early T1 to T2 oral squamous cell carcinoma. *J Surg Oncol*. 2019 Mar 15;119(4):449–454.
12. Kademani D, Bell RB. *Prognostic Factors in Intraoral Squamous Cell Carcinoma: The Influence of Histologic Grade*. 2005:1599–1605.
13. Cariati P, Martinez Sahuquillo Rico A, Ferrari L, Pampin Ozan D, Gonzalez Corcóles C, Arroyo Rodriguez S, Ferrari S, Lara IM. Impact of histological tumor grade on the behavior and prognosis of squamous cell carcinoma of the oral cavity. *J Stomatol Oral Maxillofac Surg*. 2022;123(6):e808–e813. Nov.
14. Subramaniam N, Balasubramanian D, Murthy S, Kumar N, Vidhyadharan S, Vijayan SN, et al. Predictors of loco-regional control in stage I/II oral squamous cell carcinoma classified by AJCC 8th edition. *European Journal of Surgical Oncology*. 2019;45(11):2126–2130. Nov.
15. Abu-Ghanem S, Yehuda M, Carmel NN, Leshno M, Abergel A, Gutfeld O, 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 Sep;142(9):857–865.
16. D'Cruz AK, Vaish R, Kapre N, Dandekar M, Gupta S, Hawaldar R, et al. Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer. *New England Journal of Medicine*. 2015 Aug 6;373(6):521–529.
17. Hanai N, Asakage T, Kiyota N, Homma A, Hayashi R. Controversies in relation to neck management in N0 early oral tongue cancer. *Jpn J Clin Oncol*. 2019;(2):1–9.
18. 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 Oncol*. 2014 Dec;50(12):1165–1168.
19. Girardi FM, Zanella VG, Kroef RG. Correlation between clinical and pathological data and surgical margins in patients with squamous cell carcinoma of the oral cavity. *Braz J Otorhinolaryngol*. 2013 Mar-Apr;79(2):190–195.
20. Sutton DN, Brown JS, Rogers SN, Vaughan ED, Woolgar JA. The prognostic implications of the surgical margin in oral squamous cell carcinoma. *Int J Oral Maxillofac Surg*. 2003 Feb;32(1):30–34. https://doi.org/10.1054/ijom.2002.0313.
21. Bajwa MS, Houghton D, Java K, Triantafyllou A, Khattak O, Bekiroglu F, Schache AG, Brown JS, McCaul JA, Rogers SN, Lowe D, McMahon J, Shaw RJ. The relevance of surgical margins in clinically early oral squamous cell carcinoma. *Oral Oncol*. 2020 Nov;110, 104913.
22. McMahon J, O'Brien CJ, Pathak I, Hamill R, McNeil E, Hammersley N, et al. Influence of condition of surgical margins on local recurrence and disease-specific survival in oral and oropharyngeal cancer. *British Journal of Oral and Maxillofacial Surgery*. 2003;41(4):224–231.
23. Priya SR, D'Cruz AK, Pai PS. Cut margins and disease control in oral cancers. *J Cancer Res Ther*. 2012 Jan;8(1):74–79.