Original Article

DOI: 10.7860/JCDR/2022/56672.16350

Prognostic Role of Histological Scoring of Oral Squamous Cell Carcinoma

Pathology Section

SVR RAJA SEKHAR[1], PRIYANKA PAPPALA[2], RAVI CHANDRA BONU[3], GOUTHAMI BALLI[4]

ABSTRACT

Introduction: Diagnosis of oral squamous cell carcinomas require assessment of parameters like histologic grade, tumour depth of invasion, lymphovascular invasion, perineural invasion, margin status, worst pattern of invasion, But for treatment purpose only Tumour, Nodes and Metastases (TNM) staging is given importance.

Aim: To develop a scoring system based on different histopathological tumour characteristics and to know its prognostic role in oral squamous cell carcinomas.

Materials and Methods: This retrospective study was conducted in Department of Pathology at Great Eastern Medical School and Hospital, Srikakulam, Andhra Pradesh, India, from September 2011 to August 2016 and data was followed-up for 5 years, upto August 2021. Resection of primary oral lesions with cervical lymph nodal dissection were included in the study, while cases of non squamous cell carcinomas, variants of squamous cell carcinoma, post radiotherapy cases, defaulted cases, patients who lost for follow-up were excluded. The Histoscore (H score) was obtained by the scores of all histopathological tumour characteristics and it ranged from 2-11. This H score was divided into three groups and mean survival period of these three Histoscore Groups (HS groups) were calculated for their prognostic use (Group 1 has score 2-5, Group 2 has score 6-8, Group 3 has score 9-11). Medians and ranges were used to summarise continuous data, while frequency counts and percentages were used for categorical data. Kaplan-Meier's analysis was used for evaluating 5 years survival. The p-value <0.05 was considered as statistically significant.

Results: A total of 90 cases were studied. Mean survival period was compared to HS groups, Group 1 had 64±7.59 months, Group 2 had 40.8±11.88 months, Group 3 had 26.06±12.25 months with a p-value <0.001, indicating it as a statistically significant parameter. Based on TNM staging, majority were in T2 (N=41, 45.55%), N1(N=34, 37.77%) and Mx (N=87, 96.66%).

Conclusion: Histoscore groups of the oral squamous cell carcinomas have significant differences in the mean survival period among themselves. Hence, this histoscore groups can be an additive to the TNM classification, which provide more prognostic information to the oncologists.

Keywords: Depth of invasion, Lymphovascular invasion, Oral cancer, Perineural invasion, Score, Survival

INTRODUCTION

Squamous cell carcinoma of oral cavity is one of the prevailing problems in people chewing tobacco related products [1] in developing countries like India. Its incidence is raising all over the world, accounting for 30% of all cancers [2]. The diagnosis of this tumour is confirmed only by histopathological examination. During the process of diagnosis, various parameters like histologic grade, tumour depth of invasion, lymphovascular invasion, perineural invasion, margin status, worst pattern of Invasion are evaluated generally for all the cases. Though these tumour characteristics are studied, treatment is based primarily on the Tumour, Nodes and Metastases (TNM) classification [3].

There are significant advances in different therapeutic modalities but there is no significant improvement in the 5 year overall survival rate in the last few decades [4,5,6]. This maybe due to lack of appropriate prognostic markers which could alter the treatment modalities. There are some studies [6,7,8] which recommend to include these tumour characteristics into TNM classification but it may be complicated as it has to be divided into sub groups and sub-subgroups [8]. To avoid these complications in pathological diagnosis, at the same time, to provide more information for the oncologists in a simpler manner, present study tried to develop a scoring system basing on histopathological tumour characteristics, which is an addition to TNM classification, helps the patients to get better treatment and decreases the tumour recurrences and improve the overall survival.

The present study aimed to develop a scoring system based on different histopathological tumour characteristics and to know its prognostic role in Squamous cell carcinomas of oral cavity. The Objectives:

- To reclassify the histopathological parameters as per the latest College of American Pathologists (CAP) protocol.
- To assign scores for each histopathological parameter separately.
- To obtain a Histoscore (H score) for each patient by adding the scores of all histopathological parameters.
- To categorise the H scores into three Histoscore Groups (HS Groups) and compare the mean survival periods among these three groups.

MATERIALS AND METHODS

This retrospective study was conducted in Department of Pathology at Great Eastern Medical School and Hospital, Srikakulam, Andhra Pradesh, India, from September 2011 to August 2016. The study was started in 2017 and the patients were followed-up for five years ie., upto August 2021. The study was approved from the Institutional Ethical Board (IEC:26/2017).

Sample size calculation: Sample size was 87, calculated by taking 95% confidence interval with 5% marginal error and 6% as population proportion.

Inclusion and Exclusion criteria: A total of 124 cases of Resectable primary oral lesions with cervical lymphnodal dissection were included in the study, while cases of non squamous cell carcinomas, variants of squamous cell carcinoma, post radiotherapy cases, defaulted cases, patients who lost for follow-up, which all constituted 34 cases, were excluded from the study.

Procedure

These 90 cases were followed-up for a period of five years. Data was retrieved from the records of Histopathology, Great Eastern Medical School and Hospital. All the slides and blocks were reviewed for the

various histopathological parameters like histologic grade, tumour depth of invasion, lymphovascular invasion, perineural invasion, margin status and worst pattern of Invasion as per the College of American Pathologists (CAP) protocol, version 4.1.1.0 [9].

- Histological grading of the tumour was done as well differentiated (Grade 1), moderately differentiated (Grade 2) and poorly differentiated (Grade 3) depending on the highest grade present in the tumour proper [10].
- Tumour Depth Of Invasion (DOI) is measured from the basement membrane of the adjacent normal to the deepest point of invasion of the tumour [11,12].
- Lymphovascular Invasion (LVI) and Perineural Invasion (PNI) were recorded as positive when vessels, nerves of any size were involved, irrespective of their location whether within or outside the tumour [13].
- Margins were said to be involved when the invasive carcinoma or carcinoma in-situ/High grade dysplasia is present at the margin (microscopic cut-through of tumour) [14].
- Worst Pattern of Invasion (WPOI) is graded as mentioned below [15]:

  Type 1- Pushing border

  Type 2- Finger like growth

  Type 3- Large separate islands, more than 15 cells per island

  Type 4- Small tumour islands, 15 cells or fewer, per island

  Type 5- Tumour satellites, >1 mm from main tumour or next closest satellite. Dispersed LVI or PNI.
- The Extranodal Extension (ENE) was taken as positive whenever the metastatic deposit infiltrated through the lymphnode capsule into the surrounding connective tissue.

Scoring is given for all the other histopathological tumour characteristics as per below mentioned [Table/Fig-1]. Tumour size, lymphnodal involvement and metastasis is categorised as per TNM staging.

Histopathological tumour characteristics		Score
Grade	Well (Grade 1)	1
	Moderate (Grade 2)	2
	Poor (Grade 3)	3
Depth of invasion	<5 mm	1
	5-10 mm	2
	>10 mm	3
Lymphovascular invasion	Absent	0
	Present	1
Perineural invasion	Absent	0
	Present	1
Worst pattern of invasion	1-4	0
	5	1
Margins	Uninvolved	1
	Involved	0
Extranodal extension	Absent	0
	Present	1

[Table/Fig-1]: Scoring of different histopathological tumour characteristics.

The Histoscore (H score) is obtained by adding the scores of all histopathological tumour characteristics and it ranged from 2-11. This H score is divided into three groups as per below mentioned [Table/Fig-2] and mean survival period of these three Histoscore Groups (HS groups) are calculated by taking the average number of years survived by the patients during the follow-up period of 5 years.

Histoscores	Histoscore groups
Score 2-5	1
Score 6-8	2
Score 9-11	3

[Table/Fig-2]: HS Groups for the different histoscores.

STATISTICAL ANALYSIS

Microsoft access databases were combined in Excel. Descriptive statistics were used for patients epidemiological data and histopathological features. Medians and ranges were used to summarise continuous data, while frequency counts and percentages were used for categorical data. Statistical analysis was carried by using Graphpad prism 9.3.1. Univariate and Multivariate analysis through linear regression is used for clinicopathological parameters. Kaplan-Meier's analysis was used for evaluating 5 year survival. The p-value <0.05 was considered as statistically significant.

RESULTS

A total 90 cases were studied comprising 68 (75.55%) males and 22 (24.44%) females. The age of the patients ranged from 28-72 years with peak in the 4th decade (N=35, 38.88%), followed by 3rd decade (N=27,30.00%). The clinicopathological details of these cases are tabulated in [Table/Fig-3]. Buccal mucosa (BM) was the most common site (N=42, 46.66%) in the study, followed by tongue (TG) (N=28, 31.11%), Lower Alveolus (LA) (N=8, 8.88%), Upper Alveolus (UA) (N=5,5.55%), lip (N=4, 4.44%) and Hard Palate (HP) (N=3,3.33%) as shown in [Table/Fig-3].

Parameters	Number of cases	Percentage (%)
Age (years)		
20-30	8	8.88%
31-40	27	30%
41-50	35	38.88%
51-60	11	12.22%
61-70	7	7.77%
71-80	2	2.22%
Gender		
Male	68	75.55%
Female	22	24.44%
Tumour site		
Buccal mucosa	42	46.66%
Tongue	28	31.11%
Lip	4	4.44%
Hard palate	3	3.33%
Lower alveolus	8	8.88%
Upper alveolus	5	5.55%

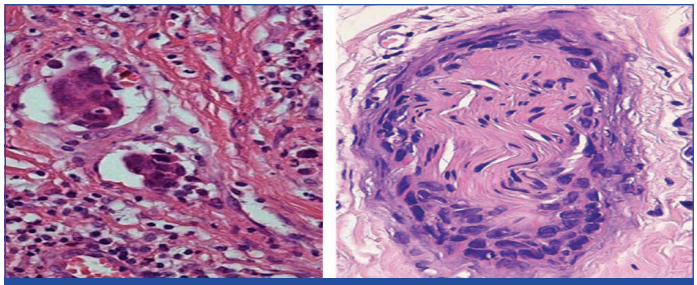
[Table/Fig-3]: Clinicopathological details of the cases.

Among these 90 cases, tumour size ranged from 0.8-6.2 cm. Based on TNM staging [Table/Fig-4], majority were in T2 (N=41,45.55%), N1 (N=34, 37.77%) and Mx (N=87, 96.66%). Grade 1 tumours were 49 (54.44%), Grade 2 tumours were 36 (40.00%) and Grade 3 tumours were only 5 (5.55%) cases. DOI is <5 mm in 13 (14.44%) cases, between 5-10 mm in 45 (50.00%) cases and >10 mm in 32 (35.55%) cases. Lymphovascular [Table/Fig-5] and perineural invasions [Table/Fig-6] are noted in 52 (57.77%) and 28 (31%) cases respectively.

The WPOI is of type 1 in 14 (15.55%) cases, type 2 in 18 (20.00%) cases, type 3 in 24 (26.66%) cases, type 4 in 12 (13.33%) cases and type 5 in 22 (24.44%) cases [Table/Fig-7]. Type 3 is the most common followed by type 5 and type 2. When compared types 1-4 with type 5, there is a significant statistical difference in prognosis. Margin is involved in two cases and but free from tumour (>5 mm)

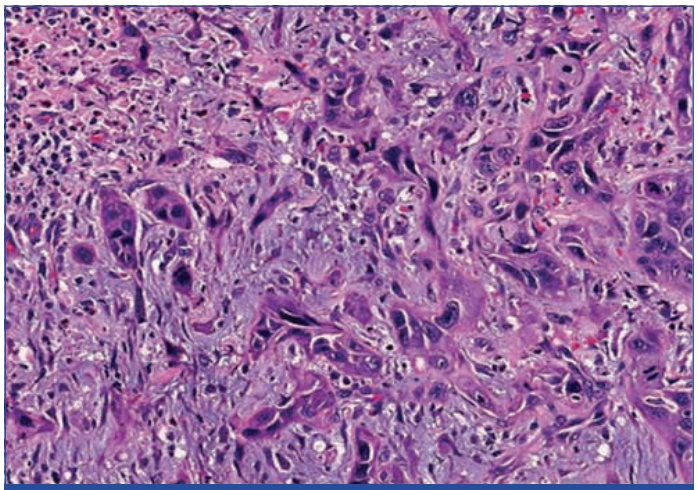
Parameters	Number of cases	Percentage (%)	Mean survival in months
Tumour size			
T1	8	8.88%	68.6
T2	41	45.55%	57.4
T3	31	34.44%	36.5
T4	10	11.11%	22.7
Lymph nodes			
N0	26	28.88%	65.2
N1	34	37.77%	54.8
N2	23	25.55%	42.9
N3	7	7.77%	21.3
Metastasis			
Mx	87	96.66%	60.9
M1	3	3.33%	15.7

[Table/Fig-4]: Tumours classification basing on TNM staging and their Mean Survival period.



[Table/Fig-5]: Tumour cells within the Lymphatic vessel and blood vessel, (H&E Stain, 40X); **[Table/Fig-6]:** Neoplastic tumour cells around the nerve bundle, (H&E Stain, 40X). (Images from left to right)

in the remaining cases. Lymphnodes were involved in 64 (71.11%) cases, while extranodal extension is seen in 15 (16.66%) cases. HS group 1 is the most common (N=58, 64.44%), followed by HS groups 2 and 3 with each of 16 cases (17.77%).



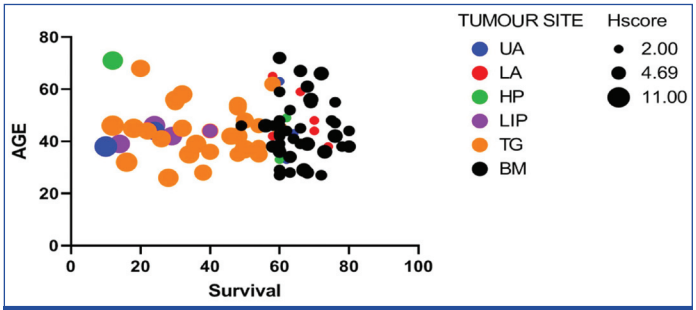
[Table/Fig-7]: Poorly differentiated squamous cell carcinoma with WPOI-5 (H&E Stain, 10X).

Mean survival period of all the above histopathological tumour characteristics are tabulated in [Table/Fig-8,9]. [Table/Fig-9] shows that most common age is 4th decade. The colour of the bubble indicates the site of the tumours, while size of the bubble corresponds to H score. Tumours with buccal mucosa site and smaller H score had better survival (in months) compared to tumours with upper alveolus, tongue site and greater H score.

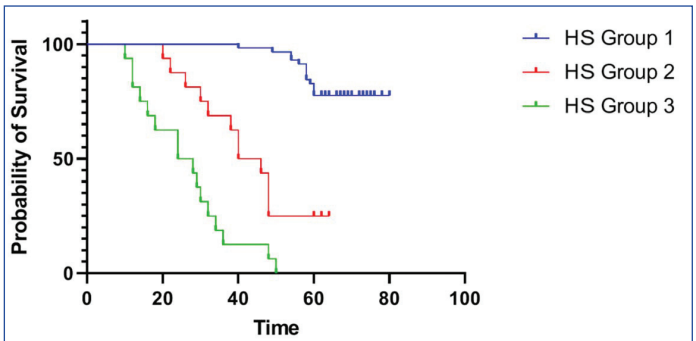
When Mean survival period was compared to HS groups [Table/Fig-10], Group 1 had 64±7.59 Months, Group 2 had 40.8±11.88 Months, Group 3 had 26.06±12.25 Months with a p-value <0.001, indicating it as a statistically significant parameter.

Parameters	Number of cases	Percentage (%)	Mean survival in months
Grade			
Well	49	54.44%	63.4
Moderate	36	40%	44.3
Poor	5	5.55%	16
Depth of invasion			
<5 mm	13	14.44%	62.9
5-10 mm	45	50%	60.3
>10 mm	32	35.55%	33.4
Lymphovascular invasion			
Present	52	57.77%	45.3
Absent	38	42.22%	63.8
Perineural invasion			
Present	28	31.11%	31.1
Absent	62	68.88%	63.0
Worst pattern of invasion			
1-4	68	75.55%	61.6
5	22	24.44%	26.9
Margins			
Involved	2	2.22%	11
Uninvolved	88	97.77%	54.10
Extranodal extension			
Present	15	16.66%	24.6
Absent	75	83.33%	58.8
Histoscore groups			
1 (Score=2-5)	58	64.44%	64
2 (Score=6-8)	16	17.77%	40.8
3 (Score=9-11)	16	17.77%	26

[Table/Fig-8]: Histopathological tumour characteristics and their mean survival period.



[Table/Fig-9]: Comparison of clinicopathological parameters with survival periods.



[Table/Fig-10]: Survival periods of different HS Groups.
*The Figure shows that HS Group1 has highest survival compared to HS Groups 2 and 3

DISCUSSION

Squamous cell carcinomas of oral cavity are one of the most common causes of morbidity in developing countries like India. Current guidelines recommend therapeutic resection of primary tumour with postoperative adjuvant therapy [3]. This adjuvant

therapy is based on the various histopathological details of the resected tumour. The parameters which measure the aggressiveness of the tumour, recurrence and metastasis of oral squamous cell carcinomas are clearly not defined. Several studies were made to identify these and included parameters like histologic grade, tumour depth of invasion, lymphovascular invasion, perineural invasion, margin status, lymphocytic host response, worst pattern of invasion [16-19]. Among these histological grade, lymphovascular invasion and perineural invasion are commonly noted in all the malignancies in general, so newer parameters like tumour depth of invasion, margin status and worst pattern of invasion were detailed in the present study.

Analysis of patients for smoking and alcohol intake was not done as previous studies [1] did not reveal any relation between them and tumour recurrence or disease-free survival. Risk scoring is simple and easy as it can be done on the routine H&E stained slides. Only the resected tumour should be commented upon pattern of invasion, as there are chances of under sampling in biopsies. The entire tumour should be submitted for microscopic examination preferably for exact evaluation of tumour invasion [8,13]. If the tumour size is >4 cm grossly, serial sections 5 mm apart should be given and sections with maximum tumour depth grossly should be submitted. In the present study, tumours having T1 had maximum mean survival period of 68.6 months and T4 had lowest mean survival period of 22.7 months.

Tumour grading, which is being done since many decades, had similar prognostic significance in this study as well, as Grade 1 had mean survival of 63.4 months and Grade 3 tumours had 16 months mean survival. DOI is a valuable parameter for predicting survival and regional nodal involvement, is measured from the basement membrane of adjacent normal mucosa to the deepest point of tumour invasion. Though the word tumour thickness is used interchangeably with DOI, there is slight difference between these two as tumour thickness is measured from mucosal surface of tumour to the deepest tumour invasion. In ulcerated tumours, DOI will be greater than tumour thickness [11,12].

Tumours with aggressive behavior have lymphovascular invasion, thereby have poorer prognosis. As in H&E stain it is difficult to different lymphatic vessel from blood vessels, authors have used the term lymphovascular invasion. Tumours without lymphovascular invasion has slightly better mean survival period (63.8 months) in the present study. But as per the previous studies, D2-40 and podoplanin [20] helps in detecting the lymphatic vessels specifically, hence they may be used for predicting the cervical lymphnodal metastasis.

The perineural invasion in the present study is reported as per latest CAP protocol irrespective of its size and location. As with previous studies [13,16], tumours in present study showing perineural invasion had poorer prognosis (31.1 months).

The status of surgical margins, particularly tumour bed margin is helpful in predicting the recurrences. In the present study, there were only two cases where the margins are involved and the mean survival period was 11 months. A shortcoming in current study is that we didn't mentioned any "Close margins", which in according to some studies is that if the tumour is <3 mm away from the resected margin. This close margin status might be helpful in predicting the recurrences [21,22].

Extranodal extension is one of the important prognostic factor and has to be commented whenever nodal deposits are present. In this study, tumours with ENE has only 24.6 months mean survival period. Even the distance of extension (> or <2 mm) from capsule is also suggested but not required for the nodal positive cases as prognosis is not dependent on distance from capsule but only those with ECE Grade 4 (any size of deposit, large or small, that was discrete and without residual nodal architecture) had poorer out comes [23].

The immunity developed by the host tissue against the tumour cells is also quantified and graded as Lymphocytic Host Response as mild, moderate and severe and is used as one of the prognostic markers in several studies earlier [15,17,18]. Though this parameter has significant role in prognosis, it is not still included in present study as it was not included in the recent CAP protocol. The lymphocytes particularly which are positive of CD3, CD8 and FoxP3 were found to have favourable prognosis [24]. More studies are required to substantiate this finding and is better if a scoring system is adapted for these immunomarkers for universal application.

Broder's grading, a modification of Byrne M et al., for prognosis of oral squamous cell carcinomas was initially based on parameters like mitotic count, nuclear atypia and keratinisation [25]. Whereas Brandwein-Gensler M et al., has introduced new prognostic marker basing on the pattern of invasion by the tumour into the underling stroma and categorised into five Worst Pattern of Invasion (WPOI) types [15]. They showed that worst patterns (patterns 5 and 4) were associated with poorer prognosis and lymphnodal metastasis. But, the recent CAP protocol (November 2021) has recommended 1-4 patterns of invasion as one group and pattern 5 as another group indicating prognostic significance for pattern 5 when compared to other patterns [9].

There are many standardised scoring systems for certain malignancies like Bloom Richardson scoring and grading system for Breast carcinoma, Gleasons scoring and grading system for prostatic carcinoma, which helps to know about their prognosis [7,17]. Similarly, some scoring systems were developed for oral squamous cell carcinomas like those published by Bryne M et al., [25] and Brandwein-Gensler M et al., [26] and Giacomarra V et al., [27]. The drawbacks of these studies were that the tumour parameters included were not clearly defined and standardised, complicated and further some of them required additional testing. The present study tried to develop a simple scoring system for oral squamous cell carcinomas on the H&E stained sections only by summating the scores given for each histopathological tumour characteristics as per the clearly defined and standardised CAP protocol version 4.1.1.0 [9] and diving them into three groups (HS groups). This study found that there was significant difference in mean survival period for these three different groups. Hence, if this scoring system is added to TNM staging, it could provide more information to the oncologists regarding the tumour aggressiveness, thereby they can alter the treatment modalities for the patients, which may finally decrease the tumour recurrences and increase the overall survival period of the patients.

Limitation(s)

This was a smaller sample size study, studies with larger cohorts are essential to substantiate our findings to make it as an additive to the TNM classification. Prognostic role of close margin status should also be considered in future studies as it was not considered in the present study.

CONCLUSION(S)

Histoscoring for oral squamous cell carcinomas is developed by summating the scores of different histopathological tumour characteristics and to further categorise them into histoscore groups which have significant differences in the mean survival period. Hence this Histoscore groups can be an additive to the TNM classification, which provide more prognostic information to the oncologists.

REFERENCES

[1] Jerjes W, Upile T, Radhi H, Petrie A, Abiola J, Adams A, et al. The effect of tobacco and alcohol and their reduction/cessation on mortality in oral cancer patients: Short communication. Head Neck Oncol. 2012;4:6.
[2] Kao SY, Lim E. An overview of detection and screening of oral cancer in Taiwan. Chin J Dent Res. 2015;18:07-12.
[3] Greene FL, Sobin LH. The TNM system: Our language for cancer care. J Surg Oncol. 2002;80(3):119-20.

[4] Safi AF, Grandoch A, Nickenig HJ, Zöller JE, Kreppel M. The importance of lymph node ratio for locoregional recurrence of squamous cell carcinoma of the tongue. J Craniomaxillofac Surg. 2017;45(7):1058-61.
[5] Bloebaum M, Poort L, Böckmann R, Kessler P. Survival after curative surgical treatment for primary oral squamous cell carcinoma. J Craniomaxillofac Surg. 2014;42(8):1572-76.
[6] Patel V, Leethanakul C, Gutkind JS. New approaches to the understanding of the molecular basis of oral cancer. Crit Rev Oral Biol Med. 2001;12(1):55-63.
[7] Po Wing Yuen A, Lam KY, Lam LK, Ho CM, Wong A, Chow TL, Yuen WF, Wei WI. 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(6):513-20.
[8] Camisasca DR, Silami MA, Honorato J, Dias FL, de Faria PA, LourençoSde Q. Oral squamous cell carcinoma clinicopathological features in patients with and without recurrence. ORL J Otorhinolaryngol Relat Spec. 2011;73:170-76.
[9] College of American Pathologists.Protocol for the Examination of Specimens from Patients with Cancers of the Oral Cavity. Version: 4.1.1.0. CAP; 2021. Available from: https://documents.cap.org/protocols/HN.Oral_4.1.1.0.REL_CAPCP.pdf.
[10] Barnes L, Eveson JW, Reichart P, Sidransky D. WHO histological classification of tumours of the oral cavity and oropharynx. In: Barnes L, Eveson JW, Reichart P, Sidransky D, eds. World Health Organization (WHO) Classification of Tumours: Pathology and Genetics of Head and Neck Tumours. Lyon: IARC; 2005:164.
[11] Ebrahimi A, Gil Z, Amit M. International Consortium for Outcome Research (ICOR) in Head and Neck Cancer. Primary tumor staging for oral cancer and a proposed modification incorporating depth of invasion: An international multicenter retrospective study. JAMA Otolaryngol Head Neck Surg. 2014;140(12):1138-48.
[12] Ridge JA, Lydiatt WM, Patel SG. Lip and oral cavity. In: Amin MB, ed. AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer; 2017.
[13] Miller ME, Palla B, Chen Q. A novel classification system for perineural invasion in noncutaneous head and neck squamous cell carcinoma: Histologic subcategories and patient outcomes. Am J Otolaryngol. 2012;33(2):212-15.
[14] Hinni ML, Ferlito A, Brandwein-Gensler MS. Surgical margins in head and neck cancer: A contemporary review. Head Neck. 2013;35(9):1362-70.
[15] Brandwein-Gensler M, Smith RV, Wang B, Penner C,Theilken A, Broughel D, et al. Validation of the histologic risk model in a new cohort of patients with head and neck squamous cell carcinoma. Am J Surg Pathol. 2010;34(5):676-88.
[16] Heroiu Cataloiu AD, Danciu CE, Popescu CR. Multiple cancers of the head and neck. Maedica (Bucur). 2013;8(1):80-85.
[17] Po WYA, Lam KY, Lam LK. 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.
[18] Sawair FA, Irwin CR, Gordon DJ. Invasive front grading: Reliability and usefulness in the management of oral squamous cell carcinoma. J Oral Pathol Med. 2003;32:01-09.
[19] Warburton G, Nikitakis NG, Roberson P. Histopathological and lymphangiogenic parameters in relation to lymph node metastasis in early stage oral squamous cell carcinoma. J Oral Maxillofac Surg. 2007;65:475-84.
[20] Van den Eynden GG, Van der Auwera I, Van Laere SJ, Colpaert CG, van Dam P, Dirix LY, et al. Distinguishing blood and lymph vessel invasion in breast cancer: A prospective immunohistochemical study. Br J Cancer. 2006;94(11):1643-49.
[21] Alicandri-Ciufelli M, Bonali M, Piccinini A. Surgical margins in head and neck squamous cell carcinoma: What is 'close'? Eur Arch Otorhinolaryngol. 2013;270(10):2603-09.
[22] Chang AM, Kim SW, Duvvuri U. Early squamous cell carcinoma of the oral tongue: Comparing margins obtained from the glossectomy specimen to margins from the tumor bed. Oral Oncol. 2013;49(11):1077-82.
[23] Prabhu RS, Hanasoge S, Magliocca KR. Extent of pathologic extracapsular extension and outcomes in patients with nonoropharyngeal head and neck cancer treated with initial surgical resection. Cancer. 2014;120(10):1499-1506.
[24] Chen WY, Wu CT, Wang CW, Lan KH, Liang HK, Huang BS, et al. Prognostic significance of tumor-infiltrating lymphocytes in patients with operable tongue cancer. Radiat Oncol. 2018;13(1):157.
[25] Bryne M, Koppang HS, Lilleng R, Stene T, Bang G, Dabelsteen E. New malignancy grading is a better prognostic indicator than Broders' grading in oral squamous cell carcinomas. J Oral Pathol Med. 1989;18:432-27.
[26] Brandwein GM, Teixeira MS, Lewis CM, Lee B, Rolnitzky L, Hille JJ, et al. Oral squamous cell carcinoma: Histologic risk assessment, but not margin status, is strongly predictive of local disease free and overall survival. Am J Surg Pathol. 2005;29:167-78.
[27] Giacomarra V, Tirelli G, Papanikolla L, Bussani R. Predictive factors of nodal metastases in oral cavity and oropharynx carcinomas. Laryngoscope. 1999;109(5):795-99.

PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Pathology, Great Eastern Medical School and Hospital, Srikakulam, Andhra Pradesh, India.
2. Associate Professor, Department of Pathology, Great Eastern Medical School and Hospital, Srikakulam, Andhra Pradesh, India.
3. Assistant Professor, Department of Pathology, Great Eastern Medical School and Hospital, Srikakulam, Andhra Pradesh, India.
4. Assistant Professor, Department of Pathology, Great Eastern Medical School and Hospital, Srikakulam, Andhra Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. SVR Raja Sekhar,
Associate Professor, Department of Pathology, Great Eastern Medical School and Hospital, Ragolu, Srikakulam, Andhra Pradesh, India.
E-mail: rajsanuvada@gmail.co

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Apr 02, 2022
- Manual Googling: Apr 18, 2022
- iThenticate Software: Apr 22, 2022 (9%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. No

Date of Submission: **Mar 26, 2022**
Date of Peer Review: **Apr 11, 2022**
Date of Acceptance: **Apr 26, 2022**
Date of Publishing: **May 01, 2022**