TO FIND THE PROGNOSTIC SIGNIFICANCE OF TUMOR MARGINS AND TUMOR DEPTH IN ORAL SQUAMOUS CELL CARCINOMAS – A PROSPECTIVE COHORT STUDY

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ABSTRACT:
BACKGROUND: OralSquamous cell carcinomas (OSCC) are the most common type of cancers contributing for around 90%. The overall survival is below 50% for these patients. Various parameters or factors have been researched and evaluated for their significant importance and critical prognostic influence in newly diagnosed in patients with OSCC .This study evaluates the significance of histopathological parameters like tumour margins and tumour depth in prognosis of OSCC
OBJECTIVES: To find the prognostic significance of the patient based on clinic-pathological parameters like tumour margins and tumour depth in overall survival of the patient.
MATERIALS & METHODS: A prospective cohort study was performed in 25 patients with biopsy proven squamous cell carcinoma of the oral cavity who presented our hospital from August 2017 to June 2019. The data collected from their histopathological reports were tumour margins of all sides and tumour depth
RESULT: Univariate analysis was applied for various clinico-pathological parameters. Out of these parameters tumour margins greater than 5 mm had p-value 0.040, tumour depth greater than 4mm had p-value 0.860 which were not statistically significant in affecting the prognosis of the patient.
CONCLUSION- Tumour margins are found to statistically significant in affecting the prognosis of the patient. Tumour depth was not found to be statistically significant but affected the survival rate of the patient and hence both the parameters must be considered for adjuvant treatment and closefollow-up.

KEYWORDS: Tumour depth, Tumour margins, OSCC, prognosis

INTRODUCTION:

Head and neck cancer, including oral squamous cell carcinoma (OSCC), are the sixth leading cancer worldwide, with an estimated 300,400 cases and 145,400 OSCC-related deaths occurring in 2012[1]. OSCC is one of the most prevalent malignancies in the developing countries and developed countries contributing to the sixth most common cancers in the world and third most common type of cancer in South Central Asia[2]. OSCC is a major public health problem in the Indian subcontinent, where it ranks among the top three types of cancer in the country. Furthermore, OSCC often causes dysfunctions in chewing and swallowing, as well as speech and aesthetic disorders, which can worsen patients' quality of life.The majority (90%) of the cases reported of OSCC is attributed to tobacco consumption in various forms, with alcohol and smoking being other attributed factors[3]. Besides, a variety of suspected risk factors such as

chronic irritation, poor oral hygiene, viral infection, occupational exposure, malnutrition as well as low fruit and vegetable diets, and genetic factors, have been proposed for the development of oral cancer[4]. The relatively high incidence of oral cancer in India is mainly because of extremely popular use of the smokeless tobacco product called gutkha and betel quid chewing (with or without tobacco), which renders its population and especially its youth to a greater risk of developing oral submucous fibrosis, a premalignant condition resulting in increased incidence of oral cancer in younger patients.

Apart from tobacco use and alcohol abuse, human papillomavirus (HPV) has recently received special attention. HPV-16 in particular has been indicated as an etiological agent for the development of a subset of OSCC, especially at the base of the tongue and the tonsillar area in the younger individuals compared to the HPV-negative counterpart[5]. Patient's age was commonly considered co-variable and was known to influence the outcome of treatment. Gender did not seem to be a significant determinant of survival for a patient with OSCC. Moore *et al*[6]. stated that 84% of patients with tumour diameter <2 cm survived a disease-free period of 3 years as compared to 52% of patients with a tumour larger than 2 cm in diameter. Woolgar[7] showed tumour depth exceeded 5 mm; the metastatic rate was 64.7%. The presence of residual carcinoma at the margins of surgical resection is an important risk factor for local recurrence in OSCC. Standard of treatment of any OSCC is surgical resection with adequate margins with postoperative adjuvant therapy as indicated. Inadequate clearance of tumour results in increased local recurrence and decreased long-term prognosis[7, 8]. Postoperative adjuvant treatment has improved the survival statistics. Many prognostic factors have been found which are known to influence the oncological outcomes in the form of 5-year survival and overall survival (OS). The literature on the management and survival of cancers in the west is widely available, but data in the Indian context is sparse. Therefore, the present study was conducted to find the prognostic significance of tumour depth and tumour margins in OS of the patient.

MATERIAL & METHODS:

a. General study details

A prospective cohort study of 25 patients with biopsy proven OSCC who presented to Tertiary care centre in Indore, Madhya Pradesh was performed from August 2017 to July 2019. Ethical approval was taken from Institutional Human Ethical Committee approval taken with Ref no-SDC/PHD/04 on 14/07/2017. The trial is registered in Clinical trial registry of India (CTRI) with no – CTRI/2018/05/014222. Informed consent was taken from all participants with audio-video visual recording and signed consents in English and Hindi (local language). There was no funding received for the study. The study was conducted according to ethical guidelines established by the declaration of Helsinki and other guidelines like Good clinical practice guidelines and those established by the ICMR.

b. Participants

Inclusion criteria – Biopsy proven OSCC with patients in between age group of 20 to 70 years were included in this cohort study. Exclusion criteria- Patients who were medically compromised and those who received treatment before were not included in the study. Tumour classification was done according to the TNM of the International Union Against cancer (UICC-AJCC). All

patients had undergone surgery. Postoperative histopathological reports (HPR) were documented in the present study.

c. Statistics

The statistical software used in the present study was IBM SPSS VERSION 20.0. Association between numerous categorical variables were statistically calculated with the help of Pearson's correlation and chi-square test. The mean comparison in the study was done using the one-way ANOVA-test. Univariate analysis of time from diagnosis of the disease to death was performed with the help of Kaplan-Meier method, and differences between these categories were estimated by the log-rank test, with the initial point being the month of diagnosis. The influence of covariates on survival of the patient was analysed by multivariate analysis (proportional hazard method). All results were considered significant if p value was less than 0.05.

d. Variables

The data collected from the HPR were pTNM staging; tumour surgical margins; tumour depth of infiltration; lymphovascular invasion; lymph node metastasis. Primary outcome was to find significance of tumour margins and tumour depth in prognosis of OSCC.

e. Study Methodology

The patients were operated and histopathology report was studied to find parameters affecting the prognosis of the patients. Patient was considered for adjuvant treatment based on the histopathology report. After the completion of the treatment, the monthly follow-upof the patients were done for 2 years and examined for any disease recurrence / metastasis. All the histopathological parameters liketumour surgical margins; tumour depth of infiltration; lymphovascular invasion; lymph node metastasis were tabulated to be find its statistical significance

RESULTS:

Total no. of patients reported – 31 patients

Patients considered in the study – 27
(Previously Treated- 3)
(Medically compromised- 1)

Patients excluded from the study- 4

Final no. of patients accepted for participation – 25

Patients alive after 2 years – 21 patients

Dead- 4 patients

Flowchart 1- Patient Flow Diagram

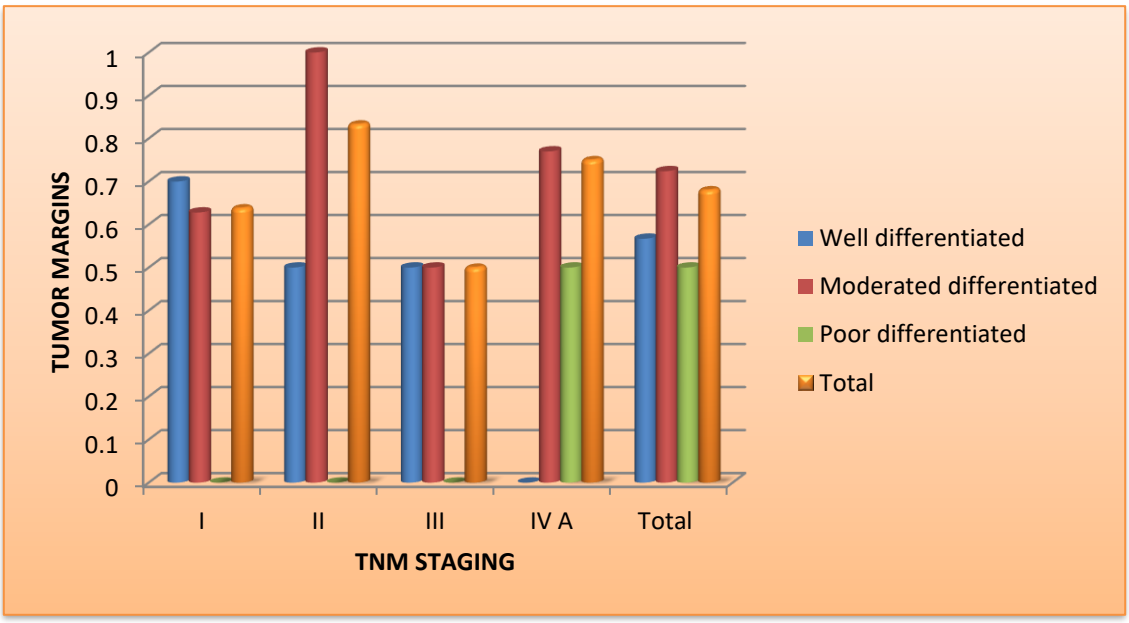
The data were analysed (Flowchart 1) and tabulated as follows,

Anova statistical analysis shows a significant correlation of TNM staging with tumour margins in different types of tumour differentiation with a p value 0.040 (Table 1)

Table no. 1: Mean value of Tumour margins (in cm) in relation with tumour differentiation in different TNM stages

TNM staging	SSC Differentiation			Total
	Well differentiated	Moderated differentiated	Poor differentiated	
I	0.7	0.628	0	0.638
II	0.5	1.0	0	0.833
III	0.5	0.5	0	0.5
IV A	0	0.77	0.5	0.75
Total	0.567	0.724	0.5	0.68

Graph no. 2: Mean value of Tumour margins (in cm) in relation with tumour differentiation in different TNM stages



One-way ANOVA statistical analysis:

source	sum of squares SS	degrees of freedom df	mean square MS	F statistic	p-value
treatment	0.1042	3	0.0347	1.8376	0.040*
error	0.2268	12	0.0189		
total	0.3310	15			

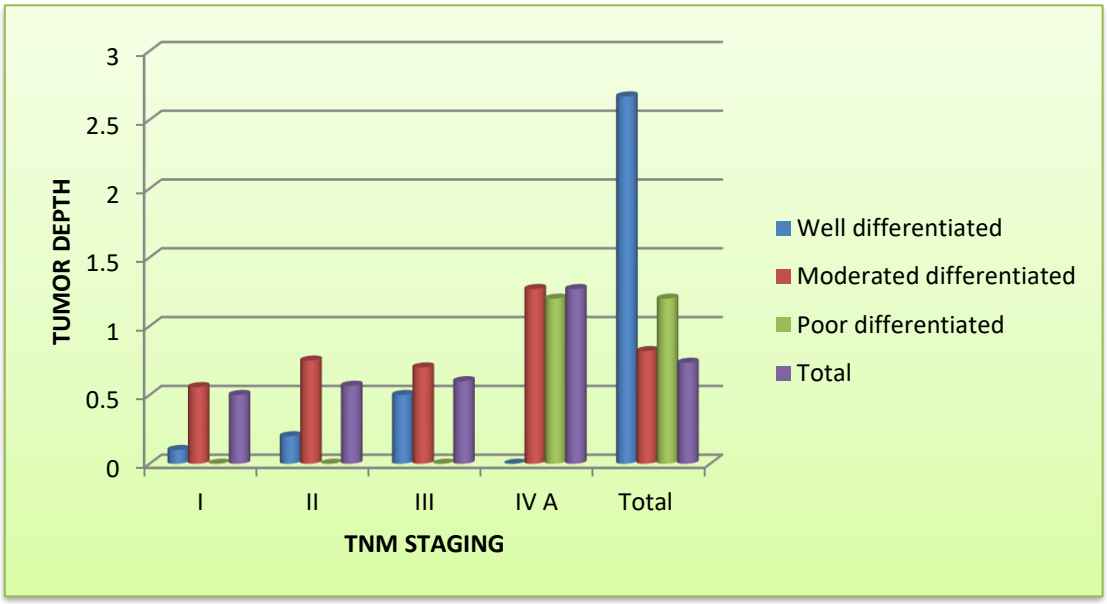
*p-value<0.05 is significant.

Anova statistical analysis shows an in-significant correlation of TNM staging with tumour depth in different types of tumour differentiation with a p value 0.860 (Table 2)

Table no. 2: Mean value of Tumour depth (in cm) in relation with tumour differentiation in different TNM stages

TNM staging	SSC Differentiation			Total
	Well differentiated	Moderated differentiated	Poor differentiated	
I	0.1	0.557	0	0.5
II	0.2	0.75	0	0.567
III	0.5	0.7	0	0.6
IV A	0	1.27	1.2	1.27
Total	2.67	0.819	1.2	0.734

Graph no. 2: Mean value of Tumour depth (in cm) in relation with tumour differentiation in different TNM stages



One-way ANOVA statistical analysis:

source	sum of squares SS	degrees of freedom	mean square MS	F statistic	p-value
treatment	0.3179	3	0.1060	0.2495	0.8602*
error	5.0975	12	0.4248		
total	5.4155	15			

Table 3 shows the 1 year survival table of the patients related to surgical margins. 3 out of 25 patients died who had less than 0.5 cm surgical margins. Table 4 shows the 1 year survival table of patients with tumour depth. 4 out of 25 patients died who had tumour depth of more than 0.4mm. Though we dint get a statistically significant value but tumour depth of more than 0.4 cm was found to influence the prognosis of the patient.

Table no. 3: Relationship of Tumour margin with prognosis of disease

Tumour margin(in cm)	Time duration (in mths)					Prognosis
	1	**3**	**6**	**9**	**12**	
<0.5	7N	6N/1D	6N/1D	4N/2D/1R	4N/3D	85.7% good prognosis rate & 14.2% mortality rate at 3 & 6 mths; 57.14% prognosis, 28.57% mortality, 14.28% recurrence rate at 9 mths. 57.14% prognosis, 42.87% mortality rate at 12 mths.
>0.5	18N	18N	17N/1R	17N/1D	17N/1D	100% good prognosis rate at 1& 3 mths 94.44% good prognosis and 5.56% recurrence rate till 6 mths 94.44% good prognosis and 5.56% mortality rate at 9 mths and 12 mths
Total	**25 N**	**24N/1D**	**23N/1D/1R**	**21N/3D/1R**	**21N/4D**	**100% good prognosis rate till 1mth; 96% good prognosis and 4% mortality at 3mths;** **92% good prognosis,4% mortality and 4% recurrence rate at 6mths;** **84% good prognosis,12% mortality and 4% recurrence rate at 9mths;** **84% good prognosis,16% mortality at 12mths;**

Table no. 4: Relationship of Tumour depth with prognosis of disease

Factors	Time duration (in mths)					Prognosis
	1	3	6	9	12	
<0.4	3N	3N	3N	3N	3N	100% good prognosis till 12mths
>0.4	22N	21N/1D	20N/1D/1R	18N/3D/1R	18N/4D	100% good prognosis rate at 1mths 95.44% good prognosis and 4.56% mortality rate till 3 mths 90.91% good prognosis and

						4.56% mortality and recurrence rate at 6mths 81.81% good prognosis and 13.63% mortality and 4.56% recurrence rate at 9mths 81.81% good prognosis and 18.18% mortality rate at 12mths
Total	25 N	24N/1D	23N/1D/1R	21N/3D/1R	21N/4D	100% good prognosis rate till 1mth; 96% good prognosis and 4% mortality at 3mths; 92% good prognosis,4% mortality and 4% recurrence rate at 6mths; 84% good prognosis,12% mortality and 4% recurrence rate at 9mths; 84% good prognosis,16% mortality at 12mths;

DISCUSSION:

The effectiveness of a surgical procedure is often assessed by its well-excluded pathological surgical margins that are considered widely to predict the need for any other kind of adjuvant treatment[9, 10]. Pathological margins are defined as margins excised surgically that are screened microscopically after shrinkage of the tissue and enlargement of the tumour. The marked decrease in frequency is approximately 9.2% -75% according to published English literature. The Royal College of Pathologists, UK classified surgical margins as follows: <1 mm is designated as involved margins, 1–5 mm is designated as close margins, and >5 mm is designated as free margins. These parameters are important in patient prognosis; however, many studies have not yet demonstrated the statistical significance of recurrence[11, 12].

Akheel et al[13] in 2020 conducted a meta-analysis of 1333 patients who had a sufficiently large sample size to conclude about two parameters affecting patients prognosis. Although this meta-analysis had failed to prove statistical evidence of any value in determining surgical margins and nodal metastasis as a direct predictor or prognosticator of OSCC, this article highlights areas of lacunae that require large scale and advanced research by multicentre global trials. This analysis clearly shows that 5 mm surgical margins often show good patient prognosis and prevent local recurrence and mortality. Surgeons should focus on surgical margins of at least 1-1.5 cm macroscopically to obtain 5 mm microscopic free of pathological margins considering tumour size and shrinkage. This study found 22% of 5 mm local recurrence or greater margins similar to the 25% which was reported by Brandwein-Gensler et al[14] showing histopathological features, responsible for the recurrence of the tumour. Detailed diagnosis of the disease on a large scale must be done at the edges closer to the primary tumour: dysplasia, carcinoma in situ, or invasive carcinoma and needed to study the prognosis of these patients.

Metanalysis by Akheel et al[15] shows that tumour depth is an effective prognosticator in OSCC to check for the presence of occult metastasis where the depth of infiltration of the tumour might be more than 4.5 mm. Moore et al[16]. Reported that the depth of tumour infiltration and the tumour thickness are not the similar terms, and clarity must be made, although many surgeons/clinicians use these both terms in a kind of similar way. The depth of the tumour infiltration indicates the rate and speed of growth in cancer in the tissue below the epithelial surface of the skin or mucosa. In cases where the epithelium is damaged, many researchers reconstruct the imaginary upper line and measure it starting from this imaginary line. Some cases, the depth of infiltration of the tumour is sometimes expressed in terms of deep, microscopic anatomic structures being achieved, rather than referring to the size of the micrometer targeted in millimetres. In the present scenario, strong collaboration between pathologists is easily made because a series of independent tests are required to determine the extent of the spread. In our study although there were no statistically significant numbers but the prognosis was affected in patients with a tumour depth of more than 4 mm[17].

Tumour thickness refers to the whole mass of the tumour where the objective parameter is required, which is usually measured by an ocular micrometre. The pathway to these blood vessels and lymphatics measures the increased risk of developing cervical metastases as it aids in the growth of tumours. Keski-Säntі et al[18]. in2007 studied 73 patients who evaluated the importance of predicting histopathologic parameters in the OSCC. They put forward that tumour depth predicted occult nodal disease, but its importance in decision-making clinically was very much limited due to ambiguity while using a limited number that provided reasonable sensitivity in diagnosing patients with nodal disease. In our present meta-analysis, the sensitivity was 84.7% at N + neck with a tumour depth of 4.5 mm[19].

Melchers et al. in 2012[20] conducted a research study in which they recommend a depth of greater 4 mm as a guide for neck dissection. Another author named Balasubramanian et al[21]. In 2014 had studied tumour depth as a prognosticatorof cervical lymph nodal metastases in the floor of mouth (FOM) and tongue cancer. They concluded that small FOM tissues of about 2.1mm –4 mm had a very high number of lymph nodal metastases. They also concluded that neck dissection must be done for FOM tumours which are greater than 2 mm thick and tongue tumours greater than 4 mm thick. In 2013, Süslü et al[22].conducted a series of case studies analysing 138 patients and concluded that tumour thickness which is greater than 8 mm and cervical lymph node metastasis were independent predictors of OS in patients with SCC. Since same levels of regional recurrence were seen in radical neck dissection (RND) and selective neck dissection (SND), supraomohyoid neck dissection(SOHND) was supported as the primary modality of treatment for patients with cN0 tissue.

Tarsitano *et al*[23]. in 2016 conducted a retrospective longitudinal study to identify the cutoff value of infiltration depth for predicting the risk of lymph node metastasis of the neck in a well-defined population of surgically treated patients affected by stage T1 to T2 oral SCC of the tongue. The mean infiltration depth of the N-negative group was found to be 2.4 mm which was substantially different from the mean value observed in the N-positive group at 5.5 mm. A meaningful cutoff was identified at an infiltration depth value of 4 mm

Studies of prognostic factors in patients with head and neck cancers almost invariably recommended that the staging system should be changed or that a prospective, randomized trial was needed to clarify the issue once and for all. Howaldt *et al*[24]. proposed a modified pTumor, Node, Metastasis staging in which three cutoffs of TT (5, 10, and 20 mm) were combined with the greatest tumor dimension to obtain the pT classification. They based their proposal on the findings in 806 patients in the large Do¨saktumor registry in Germany.

The reliability of high-resolution magnetic resonance imaging (MRI) in determining tumor depth of carcinoma of the tongue was first investigated on resected specimen. In 2001, Tetsumura *et al*[25]. found a strong correlation between the measurements obtained by MRI and histopathology, both for normal mucosa and for tumor lesions. In 2002, Iwai *et al*[26]. found a significant correlation between the tumor depth measured on the histologic specimen and what was obtained by MRI in 30 lesions of the tongue. They found significant results when they investigated the maximum tumor depth from both the surface and from a hypothetical, reconstructed mucosal line. Analogously, in 2004, Lam *et al*[27]. found a significant correlation between histologic samples and tumor depth as measured by MRI in 18 lesions (at any stage) of the tongue. They pinned each specimen to a board to prevent shrinkage of the tissue caused by the formalin fixation and digitally measured the tumor depth of both the MRI images and the histologic specimens by means of a computerized image analyzer[28].After a large number of clinical studies and research conducted by a head/ neck oncologist and oncopathologists, a latest revision of the 8 member U.S. Committee on Cancer Staging Manual in September of 2016 includes the depth of tumor infiltration as a predictor of staging of tumor. The review includes T1 tumor has a maximum size of ≤2 cm but ≤5 mm for infiltration depth. Considering the revised stage system, T2 tumors have ≤2 cm tumor but> 5 mm or tumor> 2 cm and ≤4 cm with infiltration depth and ≤10 mm. T3 tumors have size> 2 cm and ≤4 cm and> 10 mm infiltration depth or tumors> 4 cm and ≤10 mm infiltration depth.

CONCLUSION:

Growing evidence in the literature shows that tumormragins and tumor depth are reliable parameter for predicting regional node involvement and patient survival in OSCC. The substantial agreement among authors, despite the lack of comparable study groups, of measurement techniques, and cutoff values paradoxically enforced its prognostic significance.

DATA SHARING SECTION:

Individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices) are available for access. They study protocol data will be available for beginning 9 months and ending 36 months following article publication. Data will be available for the researches whose proposal of the study has been approved by an independent Institutional ethical committee. Data is available for individual participant data meta-analysis. Research proposals may be submitted up to 2 years following article publication.

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This research received no external funding.

CONFLICTS OF INTEREST:

The authors declare no conflict of interest

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