

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Evaluation of Tumor Volume and Tumor Thickness as Determinants of Lymph Node Metastasis in Oral Squamous Cell Carcinoma.

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ABSTRACT

The aim of the study was to evaluate Tumor Volume and Tumor Thickness as Determinants of Lymph Node Metastasis in Oral Squamous Cell Carcinoma -Buccal Mucosa and Gingivo-Buccal Sulcus by Radiological and Histopathological correlation. The study population consisted of 70 patients presenting to the Department of Oral and Maxillofacial Surgery, FDS, Ramaiah University of Applied Sciences, Bangalore and Dept. of Surgical Oncology, M S Ramaiah Medical College who were clinically diagnosed with Oral Squamous Cell Carcinoma (OSCC) of Buccal Mucosa (BM) and Gingivo-Buccal Sulcus (GBS) indicated to undergo surgical management, between June 2019 to April 2022. The pre operative contrast enhanced computed tomography (CECT) of the patients was used to evaluate the Tumor Volume (TV), Tumor Thickness (TT) and Lymph node Metastasis (LNM) which was then correlated with the post-operative histopathological (HPE) reports. There was a strong correlation between the radiological and pathological TV and TT which was statistically significant ($p\text{-value} \leq 0.001$). There was a weak correlation between the radiological and pathological TT and TV and its association with LNM. Also, CECT can be used effectively in predicting the LNM and the levels of LN involved. In the present study the radiological and pathological TV and TT had a weak correlation with LNM indicating that TV and TT cannot be used as independent predictors of LNM in OSCC of BM and GBS.

Keywords: Tumor volume, Tumor Thickness, Depth of Invasion, Lymph node Metastasis, Buccal Mucosa, CECT, Squamous cell carcinoma.

<https://doi.org/10.33887/rjpbcs/2023.14.4.3>

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INTRODUCTION

Oral squamous cell carcinoma is one of the most common and fatal malignancies known to human kind. Even after decades of research around the world, a definitive cure for this disease has not been forthcoming due to its high potential for local invasiveness and a great inclination for metastasis to the cervical lymph nodes. The prevalence of oral squamous cell carcinoma is reported to be highest in the South Asian region [1].

With the exception of distant metastasis, the presence of metastasis to the cervical lymph nodes in the neck has been documented as the single most important adverse independent prognostic factor of the disease and has proved to be detrimental in the overall survival rate in the squamous cell carcinoma of head and neck region. The presence of neck metastasis in oral squamous cell carcinoma is well known. Also, presence of such metastasis decreases the disease free survival rate of the patient owing to a greater chance of local or distant recurrence [2].

Various factors have been documented in the literature to effectively predict the metastasis of the primary tumor to cervical lymph nodes such as TV, TT, DOI, site of the tumor, degree of differentiation, Neutrophil-monocyte ratio, vascular and perineural invasion etc. which are independently prognostic in assessment of lymph node metastasis.

There is an increasing interest in the relationship between tumour volume and treatment outcome over the last 10-15 years. If tumour volume is to be used as an independent prognostic factor, it is imperative that the methods for volume measurement be standardised, robust and reliable.

Although used interchangeably TT and DOI are two separate entities. TT represents the distance from the tumor surface to the deepest point of invasion while DOI assesses the tumor invasiveness measured from the adjacent normal mucosal basement membrane to the deepest point of tumor invasion [3].

TT is applicable to both clinical and pathologic T-classifications, though its prognostic value is primarily derived from surgical specimens. Pre-operative, clinical and radiological evaluation is the only way to assess TV and TT to stage a tumor and also effectively predict incidence of LNM [4]. While the gold standard to measure TT is ultimately postoperative tumor thickness assessed on definitive pathology, it would be useful to establish a method to evaluate tumor thickness preoperatively [5].

Therefore, addressing the performance of a radiographic parameter compared with a criterion standard pathologic measurement is essential for validating the radiologic tool in predicting neck metastasis.

Pre-treatment CECT is one of the valuable techniques in staging of the disease, evaluation of adjacent osseous invasion and it also detects presence of cervical nodal metastasis which helps in treatment planning and post-treatment follow-up of the patients with head and neck cancer [6]. Robust data confirming the reliability of radiologic tumor volume (rTV), tumor thickness (rTT) in predicting cervical lymph node metastasis is sparse in buccal and gingivobuccal OSCC [7, 8].

Hence, our study focuses on evaluating the tumor volume and tumor thickness as determinants of LNM both radiologically and histopathologically in clinically diagnosed cases of OSCC-BM & GBS.

MATERIALS AND METHODS

The present study was conducted in the Department of Oral and Maxillofacial Surgery, Faculty of Dental Sciences, Ramaiah University of Applied Sciences, Bangalore after obtaining the institutional ethics clearance.

This retrospective study aimed to evaluate the effectiveness of Tumor volume and Tumor thickness as determinants for lymph node metastasis in OSCC-BM & GBS. Study participants selected were patients diagnosed with OSCC-BM & GBS with complete case records and patients in whom CECT was used for pre-operative assessment, from March 2021 to April 2022. Our study included 70 patients (19 males and 51 females) with a mean of 57.73 years and an age range of 31-85 years. Majority of the patients had

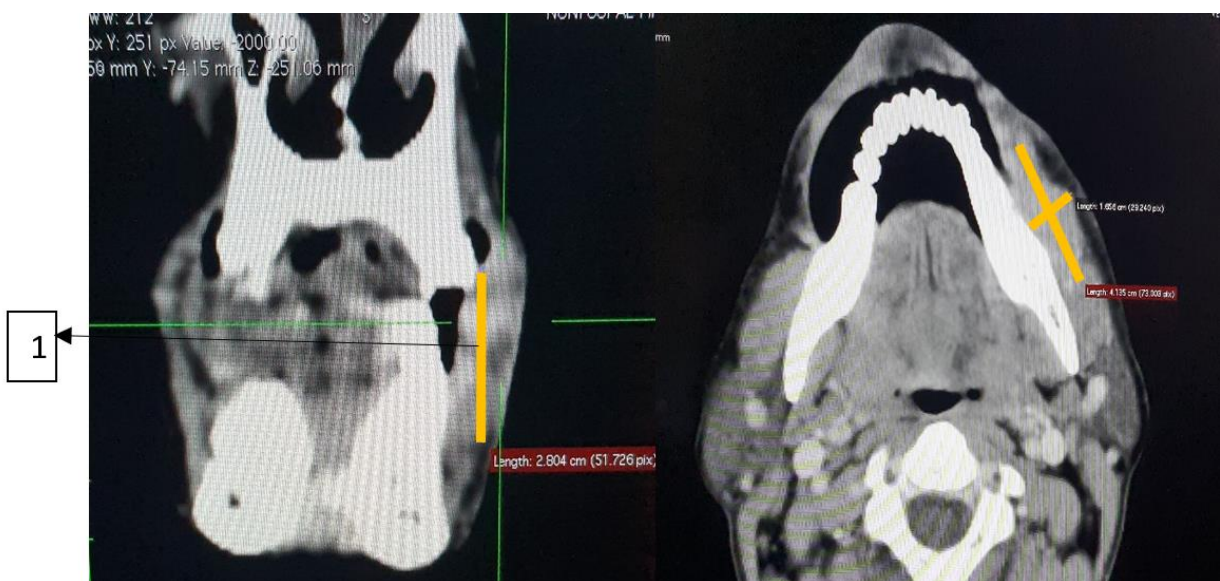
OSCC-BM followed by GBS and alveolus. The exclusion criteria included patients who have undergone preoperative radiotherapy and/ or chemotherapy, patients with history of recurrence of the disease and patients with allergy to contrast media.

For radiological evaluation the TV was calculated by multiplying all 3 of these dimensions, that is length x width x thickness. TT is determined from the tumor surface till the deepest point of tumor invasion. For BM & GBS, axial and coronal scans were evaluated because tumors had a pre-dominantly horizontal growth pattern. LNM was also evaluated with the use of CECT keeping 10mm as the cut off for short axis diameter of the lymph nodes for enlargement and enhancement. (Figure 1,2)

Figure 1: Axial section of CECT used to measure rTT in OSCC-BM where 1- The AP measurement of the lesion and 2- TS measurement of the lesion



Figure 2: Axial and Coronal sections of CECT used to measure rTV where 1- CC extension of the tumor)



Pathological slides stained with haematoxylin and eosin were reviewed by expert pathologists and all cases were classified accordingly to the 8th AJCC staging system. For each patient, the pathologists described tumoral grading, dimensions, TT, TV and LNM. pTT was measured in millimeters (mm) from the tumor surface till the deepest point of tumor invasion.. The tumor volume was calculated by multiplying all 3 dimensions, that is length x width x thickness. LNM -as positive/negative, and level of involved lymph nodes will be recorded as per the HPE report.

Correlation of the radiological and histopathological findings of TV & TT will be done to determine the LNM in OSCC-BM & GBS.

For statistical analysis Chi Square Test was used to correlate b/w Radiological Lymph Node Metastasis with Tumor Size & Thickness & also the same with pathological methods. Mann Whitney Test was used to compare the mean Radiological & Pathological Tumor Volume & Thickness based on Lymph node Metastasis and also between Radiological Tumor Volume & Thickness and Pathological Tumor Volume and Thickness. The level of significance was set at $P < 0.05$.

RESULTS

On radiological evaluation patients with a TV of $< 15 \text{ cm}^3$ have a relatively higher association (69.6%) with the presence of LNM as compared to patients without LNM (62.5%). A higher percentage of patients with TV of $> 30 \text{ cm}^3$ were not associated with LNM (25%). This association of radiological TV with the presence/absence of LNM is statistically insignificant ($p\text{-value} = 0.75$). Patients with a TT of $> 30 \text{ mm}$ (19.6%) and $< 10 \text{ mm}$ (60.9%) have a relatively higher association with the presence of LNM as compared to patients without LNM (12.5% and 54.2% respectively). Greater percentage of patients with TT of 10-20 mm and 20-30mm were not associated with LNM (16.7%). This association of the radiological TT with the presence /absence of LNM is statistically insignificant ($p\text{-value} = 0.50$) (Table 1). Patients with mean TV (19.50 ± 28.82) had a higher incidence without LNM as compared to TV (22.81 ± 39.74) with LNM. This difference in the mean radiological TV based on the presence or absence of LNM is statistically insignificant ($p\text{-value} = 0.55$). The mean TT of (18.54 ± 32.52) had a higher incidence without LNM as compared to TT (17.45 ± 25.84) with LNM. This difference in the mean radiological TT based on presence /absence of LNM is statistically insignificant ($p\text{-value} = 0.89$). (Table 3).

Table 1: Correlation b/w Radiological Lymph Node Metastasis with Tumor Volume & Thickness using Chi Square Test

Variable	Category	Present		Absent		p-value
		n	%	n	%	
Tumor Volume	$< 15 \text{ cm}^3$	32	69.6%	15	62.5%	0.75
	15-30 cm^3	6	13.0%	3	12.5%	
	$> 30 \text{ cm}^3$	8	17.4%	6	25.0%	
Tumor Thickness	$< 10 \text{ mm}$	28	60.9%	13	54.2%	0.50
	10-20 mm	6	13.0%	4	16.7%	
	20 -30 mm	3	6.5%	4	16.7%	
	$> 30 \text{ mm}$	9	19.6%	3	12.5%	

Table 3: Comparison of mean Radiological Tumor Volume & Thickness based on Lymph node Metastasis using Mann Whitney Test

Variable	LN Invasion	N	Mean	SD	Mean Diff	p-value
Tumor Volume	Present	46	22.81	39.74	3.31	0.55
	Absent	24	19.50	28.82		
Tumor Thickness	Present	46	17.45	25.84	-1.09	0.89
	Absent	24	18.54	32.52		

On pathological evaluation, higher percentage of patients with TV of 15-30 cm^3 were associated (50%) with LNM as compared to without LNM (45%). Patients with TV of $> 30 \text{ cm}^3$ were associated without LNM (20%) as compared to patients with LNM (10%). This association of the pathological TV with presence/absence of LNM was statistically insignificant ($p\text{-value} = 0.52$). A higher percentage of patients

with TT of 20-30mm(16.7%) were associated with the presence of LNM . Patients with a TT of <10mm and 10-20mm were associated with absence of LNM (40% and 47.5% respectively). This association of the pathological TT with presence/absence of LNM is statistically insignificant (p-value=0.38) (Table 2).

Table 2: Correlation b/w Pathological Lymph Node Metastasis with Tumor Volume & Thickness using Chi Square Test

Variable	Category	Present		Absent		p-value
		n	%	n	%	
Tumor Volume	< 15 cm ³	12	40.0%	14	35.0%	0.52
	15-30 cm ³	15	50.0%	18	45.0%	
	> 30 cm ³	3	10.0%	8	20.0%	
Tumor Thickness	< 10 mm	10	33.3%	16	40.0%	0.38
	10-20 mm	14	46.7%	19	47.5%	
	20 -30 mm	5	16.7%	2	5.0%	
	> 30 mm	1	3.3%	3	7.5%	

The mean TV without LNM was significantly higher (20.33±11.03) as compared to TV with LNM (18.47±10.42) . This difference in the mean radiological TV based on the presence or absence of LNM is statistically insignificant (p-value=0.58) . The mean TT when assessed pathologically with presence/absence of LNM was higher without LNM (13.25±10.47) as compared to TT with LNM (14.33±8.58). This difference in the mean pathological TT is statistically insignificant (p-value=0.41).(Table 4)

Table 4: Comparison of mean Pathological Tumor Volume & Thickness based on Lymph node Metastasis using Mann Whitney Test

Variable	LN Invasion	N	Mean	SD	Mean Diff	p-value
Tumor Volume	Present	30	18.77	10.42	-1.56	0.58
	Absent	40	20.33	11.03		
Tumor Thickness	Present	30	14.33	8.58	1.08	0.41
	Absent	40	13.25	10.47		

Radiological co-relation of TV(rho=0.23, p-value=0.04) and TT (rho=0.10, p-value=0.42) with LNM showed a significant positive weak correlation with the TV and a very weak correlation with TT. This correlation was statistically significant for rTV and insignificant for rTT. Pathological co-relation of TV(rho=0.05, p-value=0.67) and TT (rho=0.15, p-value=0.20) with LNM showed a significant positive weak correlation with pTV and very weak correlation with pTT . This correlation was statistically insignificant for both the parameters.

The TV when assessed radiologically and pathologically showed a strong positive correlation (rho=0.74) which is statistically significant (p-value=<0.001). The TT when assessed radiologically and pathologically showed a very strong correlation (rho=0.88) which is also statistically significant (p-value=<0.001).(Table 5)

Table 5: Spearman's correlation test to assess the relationship b/w Radiological & Pathological Tumor Volume & Thickness

Method	Tumor Volume		Tumor Thickness	
	rho	p-value	rho	p-value
Radiological & Pathological	0.74	<0.001*	0.88	<0.001*

The distribution of the levels of Lymph nodes involved was done both radiologically and pathologically where it was seen that Level 1b(45.7 % & 25.7%) ,level 1a (27.2% & 12.8%) , and Level 2a (25.7% & 12.9%) are the most commonly involved levels of lymph nodes in OSCC-BM & GBS.

DISCUSSION

Oral squamous cell carcinoma (OSCC) is the sixth most common cancer worldwide and the most common site of malignancy in the head and neck. OSCC is primarily treated by wide local excision and neck dissection in early stages followed by adjuvant chemotherapy and radiation therapy in the advanced stage. The TNM classification has traditionally been used as an objective, internationally accepted system for the assessment of OSCC [9-11]. However, several studies have shown that many factors other than size, node involvement, and metastasis have varying degrees of influence on the prognosis [12].

In our study, we attempted

To assess the TV, TT and Lymph node metastasis by CECT and histopathologically in OSCC- BM and OSCC-GB. Radiologic-Pathologic Correlation of TV & TT and their significance in predicting lymph node metastasis in OSCC of the BM and GBS and to assess the efficacy of pre-treatment CECT in predicting the LNM in OSCC -BM and GBS.

Thomas Mücke *et al* in their study on Influence of tumor volume on survival in patients with oral squamous cell carcinoma involving tongue recorded the mean primary tumor volume radiologically as 7.14 cm³ with a range of 1.3–24.21 cm³ [4]. In comparison to our study wherein the TV for patients with OSCC-BM & GBS were recorded, a mean radiological TV of 22.81 ± 39.74cm³ was associated with the presence of LNM and a mean TV of 19.50±28.82cm³ (n=24) without LNM, which was statistically insignificant (p value=0.55). This variation in the mean TV is because of the different subsites selected in our study including all T Stages of the tumour as compared to the study done by Thomas Mücke *et al* where only early OSCC- tongue cases were evaluated.

Young-Hoon Joo *et al* in their study reported that the mean tumor volume was 27.7 cm³ and a significant positive correlation was found between radiological tumor volume and cervical lymph node metastasis (P<0.001). They also reported that when the tumor volume exceeded 20 cm³, the cervical metastasis rate increased to 69.2% [10].

J. Madana *et al* conducted a study where they reported that the correlation between CT scan-based tumor thickness and surgical specimens based thickness was significant.(13) Similarly in our study we performed a spearman's test to determine the correlation between rTT and pTT and found that there is a very strong correlation between the two parameters which is statistically significant(rho=0.88, p-value=<0.001) [14].

Kiran B. Jadhav *et al* conducted a review where they reported that when the TT exceeded 5 mm, the metastatic rate was 64.7%. and when TT was less than 5 mm, the incidence of cervical metastasis was only 5.9%. They suggested that there is a discerning point at 5 mm of TT at which cervical metastasis was probable [15]. Pandeshwar P *et al* conducted a study where they reported that on using a nodal size of 1 cm and the presence of central nodal necrosis (CNN) as radiological criteria for nodal metastasis CT scanning staged 23 of the 27 histopathologically positive necks, providing accuracy of 88%, sensitivity of 92%, and specificity of 84% in detection of nodal metastasis. In comparison to our study where we reported that CECT was 90.66% sensitive in diagnosing LNM and 96.84 % sensitive for diagnosis of the levels of lymph node involved.

To summarize, the results of this study indicate that

There is a significant correlation between the radiologically and histopathologically assessed TV and TT which can be useful for treatment planning. Since there is a weak correlation between radiological and pathological TV, TT and its association with LNM, these parameters can be used with other diagnostic criteria for predicting lymph node metastasis. CECT can be used effectively in predicting the LNM and assessing the levels of cervical lymph nodes involved.

Some limitations of the present study include; retrospective design, heterogenous data (all T sizes included) and incomplete records, leading to reduction in cohort size and the impact of the study.

CONCLUSIONS

In conclusion, in the present study there was a significant strong correlation between radiological and histopathological Tumor Volume and Tumor Thickness in OSCC of buccal mucosa and gingivobuccal sulcus, which can be useful in treatment planning. The radiological and pathological Tumor Volume and Tumor Thickness had a weak correlation with LNM which indicates that Tumor Volume and Tumor Thickness cannot be used as independent predictors of LNM in OSCC of BM and GBS. However, Tumor Volume and Tumor Thickness can be used as one among the other prognostic factors to predict the LNM. There is a definite requirement for an accurate measurement tool and a standardized measurement technique amongst radiologists and pathologists to evaluate the TT and TV. A prospective design with a larger cohort and collaborative effort may help in arriving at more significantly conclusive results on the usefulness of TT and TV as predictors of LNM in OSCC of BM and GBS.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge Dr Santosh for the statistics and the technical team from the radiology and surgical oncology department for their constant help and support.

Ethical Approval

The present study was conducted in the Department of Oral and Maxillofacial Surgery, Faculty of Dental Sciences, Ramaiah University of Applied Sciences, Bangalore after obtaining the institutional ethics clearance.(Ref.no: EC-2021/PG/067).

Informed Consent:

This article does not include any human studies.

Authors Contribution

Dr Sushant: Conceptualization, writing, methodology, interpretation, Dr Kavitha Prasad: Conceptualization, methodology, editing, reviewing, Dr Aakash: Methodology, reviewing, interpretation, reviewing, Dr Arvind: Supervision, reviewing, Dr Harish: Supervision, administration, Dr K Ranganath: Supervision, administration.

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