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ORIGINAL ARTICLE

Evaluation of Tumour Volume as a Prognostic Factor in Carcinoma Buccal Mucosa

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Abstract (1) To determine tumor volume by clinical measurement, imaging and histopathological examination in patients with squamous carcinoma of buccal mucosa. (2) To correlate tumor volume with lymph-node metastasis and loco-regional control. Retrospective Observational Study. Rural tertiary care hospital. 75 Patients undergoing surgery for T2 (68%) and T3 (32%) Oral squamous carcinomas were included in this observational study. Tumor volume—a product of maximum length, breadth and thickness, was determined clinically and by imaging. Tumor volume on histopathology was documented and correlated with lymph-node metastasis. After 13 months minimum follow-up, tumor volume was correlated with loco-regional control. Recurrences were analysed with regard to tumor volume, depth of invasion, lymph-node metastasis and resection margins. Average tumor volume was 7.1 cm^3among T2 and 14.4 cm^3among T3. 25% of T2 tumors had metastatic lymph-nodes compared to 33.3% in T3. There was positive correlation between tumor volume and lymph-node metastasis. Lymph-node metastasis was absent when tumor volume was < 8 cm^3. There were 4 local and 2 regional recurrences in this study. Average histopathological tumor volume among patients who had local recurrence was 12.95 cm^3. Regional recurrences occurred in tumors staged N2b and N3b on histopathology. Average depth of invasion in patients with recurrence was 10.33 mm.. Tumor volume represents actual tumor load and correlates with lymph node metastasis and prognosis in oral cancers. Depth of invasion and tumor thickness influence staging and prognosis. Large volume tumors have poor oncological outcome.

Keywords Tumour volume · Buccal mucosa · Squamous cell carcinoma · Tumour thickness · Depth of invasion · Lymph node metastasis

Introduction

Head and neck cancers account for 30–35% of all malignancies in India and oral cancers constitute almost 50% of head and neck malignancies [1]. 80% of these patients present with advanced disease in our region. Therefore, Head and Neck cancers are a major public health problem in developing countries due to addictions and change in life style [2].

Treatment protocol and prognosis vary widely and are based on the TNM staging of the disease at the time of diagnosis. Till 2017 Tumour (T)—was classified by a subjective and two-dimensional measurement. However, From 2018 Depth of invasion has been incorporated in T-classification. T-classification fails to define the true three-dimensional volume which is more accurate in depicting tumour load [3].

The five years overall survival in these patients with locally advanced lesions is only about 50%. The major cause of morbidity and mortality in these patients is loco-regional recurrence. Therefore, it is important to identify

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patients who are at a higher risk for loco-regional recurrence, so that aggressive treatment can be given to them. Large volume tumours have a necrotic core which does not respond to radiotherapy. Surgical resection of such tumours and adjuvant radiotherapy is also challenging due to close proximity to important structures and wider field for adjuvant radiotherapy.

Studies in literature have shown that tumor volume is an important prognostic factor in oral cancer. Tumor volume estimation can be done easily by imaging, clinical examination and histopathology. This information plays a major role in selecting treatment and adjuvant treatment and follow up [3].

Therefore in this study we estimated tumor volume by clinical examination, imaging and histopathological examination of resected specimen in 75 patients with T2 and T3 squamous cell carcinoma of buccal mucosa undergoing surgery and documented the lymph node metastasis and outcome in these patients with regards to loco-regional control.

Objectives

(1) To determine tumour volume by clinical measurement and imaging, and by histopathological examination of the resected specimen in patients with squamous cell carcinoma of buccal mucosa.
(2) To correlate the tumour volume with lymph node metastasis and loco-regional control.

Materials and Methods

Ethical clearance obtained (SDUMC/KLR/IEC/25/2019–2020). 75 Patients who underwent surgery for Squamous cell carcinoma of buccal mucosa staged T2 and T3 (Fig. 1) at Department of Otorhinolaryngology and Head and Neck Surgery in our hospital from December 2017 to May 2019 were included in this study. T4a malignancies were excluded from the study as skin or bone involvement adversely affects the outcome and will not allow evaluation of tumour volume as independent prognostic factor. Oral tongue cancers were excluded.

An informed written consent was obtained from all the patients, after proper counselling regarding the procedure being performed and the research being done. Detailed clinical history was elicited with emphasis on addictions. All the patients were clinically examined and findings like size, site, extent and clinical depth of the tumour were documented. Clinical details of cervical lymph nodes if any were documented.

Biopsy of the tumour was done and the histopathological findings were noted. Contrast Enhanced CT scan was done, maximum dimensions in antero-posterior direction, supero-inferior direction and transverse diameter were documented (Fig. 1) and primary tumour volume was calculated. All these details were entered in SPSS (version 22) excel sheet. Clinical staging was done incorporating the imaging findings.

Patients underwent wide excision of the primary tumour with adequate margins, along with marginal or hemi-mandibulectomy along with neck dissection, according to the clinical staging (Fig. 2). Marginal mandibulectomy (5 patients) was done when there was when lesion was found abutting the mandible on CT-scan and height of the mandible was adequate. Hemi-mandibulectomy (52 patients) was done when lesion found to be suspicious of mandible erosion on CT-scan, when mandibular body height was inadequate (edentulous) and the primary lesion was adjacent to last two molar tooth where marginal mandibulectomy cannot be done. Wide excision of the tumour when the primary tumour was away from alveolus (18 patients). Modified Radical neck dissection saving the accessory nerve and Internal jugular vein was done in 63 patients and Supra-omohyoid neck dissection was done in 12 patients staged N_0.

Immediately after resection of the specimen maximum length, maximum breadth and tumour thickness of the

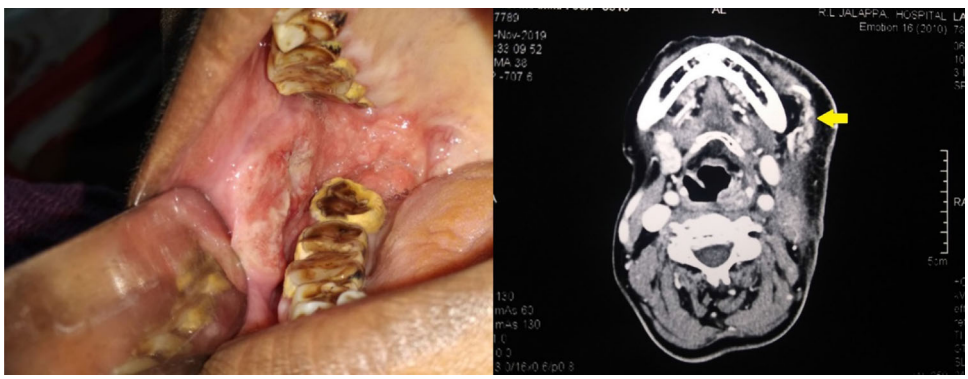

Fig. 1 Lesion involving the right buccal mucosa posteriorly extending to RMT (T3) and Axial section of CECT—showing enhancing lesion in left buccal mucosa posteriorly going to RMT

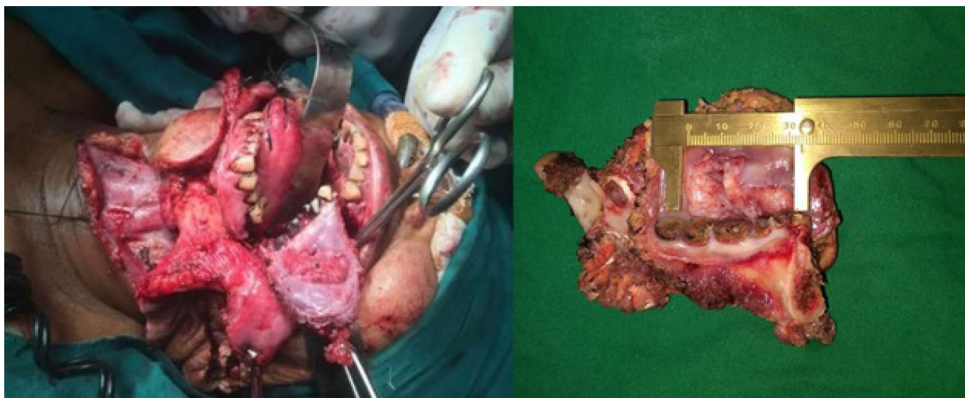

Fig. 2 Showing wide excision of primary tumor and tumor breadth Measurement using callipers

tumour was measured using callipers and clinical tumour volume (which is the product of maximum length, breadth and tumour thickness) was calculated (Fig. 2) before formalin fixation. Primary tumour and neck dissection specimen were sent for histopathological examination. Pathological staging was done and tumour volume based on histopathological examination was documented. Tumour volumes measured clinically (before formalin fixation), radiologically and by histopathological examination were compared and site and number of metastatic lymph nodes in neck were documented. Adjuvant treatment in form of post-operative radiotherapy was administered in 48 patients (64%) and 20 patients (26.67%) who had close margins or deep involvement of muscles of mastication received post-operative chemotherapy and radiotherapy. In these 20 patients Cisplatin (three weekly) was used. 7 patients (9.33%) who had T2 disease without any adverse features on histopathology did not receive any adjuvant treatment.

All patients were followed up for a minimum period of 13 months after completion of treatment and the outcome of treatment in form of loco-regional control was documented. The tumour volume was correlated with lymph node metastasis and loco regional control. The recurrences were analysed with regard to tumour volume, depth of invasion, lymph node metastasis and adequacy of resection margins. Categorical data was represented in the form of Frequencies and proportions. Chi-square test or Fischer's exact test (for 2×2 tables only) was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. Independent t test was used as test of significance to identify the mean difference between two quantitative variables. ANOVA was used as test of significance to identify the mean difference between more than two quantitative variables.

Results

In our study majority of the patients were in the age group of 45–65 years and 77% of subjects were females with a male: female ratio is 1:3.3. All patients in our study were addicted to chewable tobacco (tobacco quid). In our study 51 patients were staged T2 and 24 were staged T3. Almost all patients staged T2 had one tumour diameter between 3.5 and 4 cm. The site of primary tumour was buccal mucosa in 72%, lower gingivo-buccal sulcus in 19% and retromolar trigone in 9% of patients. The average tumour volume of T2 tumours clinically (before formalin fixation) was 12.7 cm^3, radiologically was 10.5 cm^3 and on histopathology it was 7.1 cm^3. The average tumour volume of T3 tumours on radiology was 22.6 cm^3, clinically 24.2 cm^3, histopathology it was 14.4 cm^3. Among T2 tumours 25% were found to have metastatic cervical lymph nodes and among T3 tumours 33.3% were found to have metastatic lymph nodes.

In our study, on histopathological examination of the resected specimen following formalin fixation, none of the patients had positive margins. However, close margin (< 5 mm after formalin fixation) was found in 30 patients. In majority of these 30 patients the closest margin was posterior (12) and superior (15). In our study, on histopathological examination of the neck dissection specimens, in 72% of subjects had no positive lymph nodes, 17% of subjects had 1 metastatic lymph node in submandibular region, 5% of subjects had 2 metastatic lymph nodes in submandibular region, 3% of subjects had 3 and 4 metastatic lymph nodes respectively in submandibular and upper deep jugular regions. Average histopathological tumour volume when lymph nodes were positive was 11.25 cm^3 and when the lymph nodes were negative was 7.7 cm^3 (Table 1). None of the patients in our study with tumour volume less than 8 cm^3 had metastatic lymph node.

In our study, there were 6 recurrences which occurred within a period of 6 months during follow up. Average

Table 1 Tumour volume with pathologically positive lymph nodes

Tumor volume	Lymph node status				*P* value
	Negative		Positive		
	Mean (in cm^3)	SD (in cm^3)	Mean (in cm^3)	SD (in cm^3)	
CT volume	13.0681	12.7041	15.1493	10.4445	0.556
Clinical volume	14.0628	11.1008	19.0886	9.3564	0.071
Histopathological volume	7.6912	7.7720	11.2545	5.9777	0.062

histopathological tumour volume among patients who had local recurrence was 12.95 cm^3 (Table 2). The 2 patients with regional recurrence were staged N2b and N3b on histopathology of the resected specimen. The depth of invasion in patients with recurrence had a range of 7–14 mm with average of 10.33 mm.

In our study, there were 3 deaths due to local recurrence and 2 deaths due to regional recurrence. These patients presented late and could not be salvaged. 1 patient with local recurrence is on palliative chemotherapy (Fig. 3).

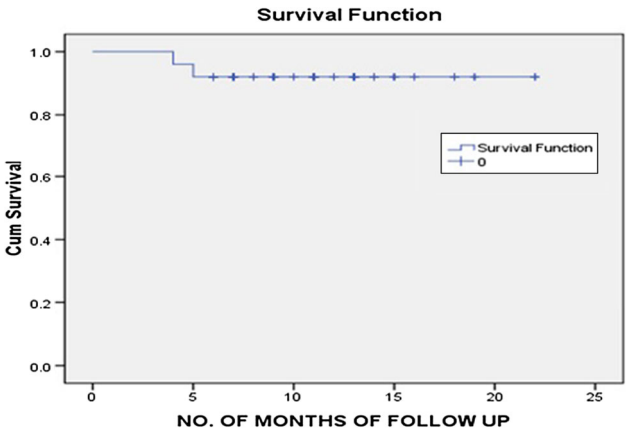

Fig. 3 Survival chart

Discussion

In this observational study, we aimed to correlate the tumour volume with metastasis to regional lymph nodes and loco-regional control after treatment. In our study, majority of the patients were elderly females. This can be attributed to the addiction to chewable tobacco quid among the women in this region. Similar observations were made in other studies in this region [4, 5]. The patients with skin or bone involvement were excluded from the study as these two variables can adversely affect the outcome and can be confounding factors. Though the study included T2 tumours also, majority of the subjects had at least one diameter of the tumour between 3.5 and 4 cm (close to T3). There was no statistically significant difference between mean tumour volume calculated clinically (before formalin fixation) and radiologically. Tumour volume when determined on histopathology was less compared to tumour volume calculated by clinical method and on radiology. This can be explained by the fact that shrinkage of the tissues occur following formalin fixation which can be about 30% [5].

In our study, majority of the patients had pathological T2 (68%) tumours, the rest had T3 tumours (32%). We observed that cervical lymph node metastasis was found in 25% of patients with T2 disease and 33.3% of patients with T3 disease. In our study, average tumour volume of T2 tumours on histopathology was 7.1 cm^3 and in T3 tumours was 14.4 cm^3. Patients who had recurrences were found to have average tumour volume more than 8 cm^3 on histopathology. Average histopathological tumour volume among patients who had local recurrence was 12.95 cm^3. The 2 patients with regional recurrence were staged N2b and N3b on histopathology of the resected specimen. The

Table 2 Mean tumor volume in subjects who survived with Subjects who had Recurrence

Tumor volume	Survived		Recurrence		*P* value
	Mean (in cm^3)	SD (in cm^3)	Mean (in cm^3)	SD (in cm^3)	
CT volume	13.5058	13.2425	15.3187	16.7806	0.757
Clinical volume	15.2402	12.3183	18.1125	16.6044	0.536
Histopathological volume	8.5880	7.5624	9.8493	6.4869	0.694

depth of invasion in patients with recurrence had a range of 7–14 mm with average of 10.33 mm. In few European studies, the primary tumour volume varied from 1.3 to 24.2 cm^3, volume of 18.3 cm^3 was taken as a cut off for large volume tumours, these large volume tumour had 5-year disease free survival of less than 40% [6]. In a study done in Brazil, tumour volume of more than 33.5 cm^3 was observed as an indicator of poor prognosis [7]. In a study done in southern India tumour volume of more than 6 cm^3 for squamous cell carcinoma of oral cavity was associated with poor prognosis and higher chances of lymph node metastasis and extracapsular invasion [8]. Our observations were similar to other studies in literature where tumour volume was found to have positive correlation with the lymph node metastasis. However, the histopathological tumour volume of more than 8 cm^3 in our study was associated with lymph node metastasis unlike other south Indian study were 6 cm^3 tumour volume was the cut off for aggressive disease. This could be because our study included buccal mucosa cancers only. Unlike Brazilian study a relatively smaller tumour volume (average 12.95 cm^3) was associated with recurrences in our study.

Depth of invasion of more than 5 mm was a bad prognostic factor in our study. All 6 patients who recurred in our study had depth of invasion more than 7 mm. According to 8th edition of AJCC staging system, depth of invasion more than 5 mm is considered locally aggressive disease and depth of invasion more than 10 mm is considered advanced disease. In our study thickness of the tumour was more as the T stage increased. The mean tumour thickness in T2 on histopathology 10.3 mm, in T3 tumours it was histopathology 14 mm. Various other studies in southern India and western countries have shown that depth of invasion of greater than 4 mm in case of malignancy of tongue correlated with poor prognosis and higher frequency of lymph node metastasis [8, 9]. However, there are very few studies which have addressed Depth of invasion in buccal mucosa cancers which are more common in our country.

Depth of invasion (DOI) in oral cavity cancer is important in determining prognosis. DOI of 7.25 mm was most predictive for occult nodal disease and 8 mm for overall survival and disease free survival. DOI was an independent predictor of overall survival and disease free survival [10]. Lymph node metastasis in patients with oral cancer of a thickness 2.1–4 mm was only 11.2%, whereas, in patients with oral cancers having tumour thickness of 4.1–6 mm lymph node metastasis was found to be 38.5% [10]. Various studies have advocated neck dissection when depth of invasion is more than 4 mm as the probability of occult cervical metastasis is greater than 20%. With increasing depth of invasion particularly > 10 mm, there is significantly increased risk of occult nodal metastasis (53%) and decrease in 5 year survival to 45% [11].

In our study, tumour volume correlated with lymph node metastasis and recurrence. Thickness of the tumour also had a positive correlation with lymph node metastasis, as tumour thickness is indirectly contributing to tumour volume. Depth of invasion more than 5 mm was a poor prognostic factor. Close margins of resection (< 5 mm after formalin fixation) was found to be another bad prognostic factor.

Conclusion

Tumour volume is a reliable indicator of tumour load and therefore has a significant impact on prognosis in buccal mucosa cancers, when adverse factors like skin and bone involvement are excluded. Depth of invasion is also an important factor in staging and prognosis. Tumours with larger volume have a higher chance of recurrence. Tumours volume more than 8 mm have a higher frequency of lymph node metastasis. Tumour thickness also correlated with lymph node metastasis. Recurrence were higher when tumour volume was more than 8 mm or when depth of invasion of more than 5 mm.

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Author contributions HSB: data collection, preparation of manuscript; SMAM: concept and design, operating surgeon, data analysis, critical review; TNS: data analysis, critical review.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval Institutional Ethics Committee, Sri Devaraj Urs Medical College—Ethical clearance obtained (SDUMC/KLR/IEC/25/2019–2020).

Human and Animal Rights None.

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