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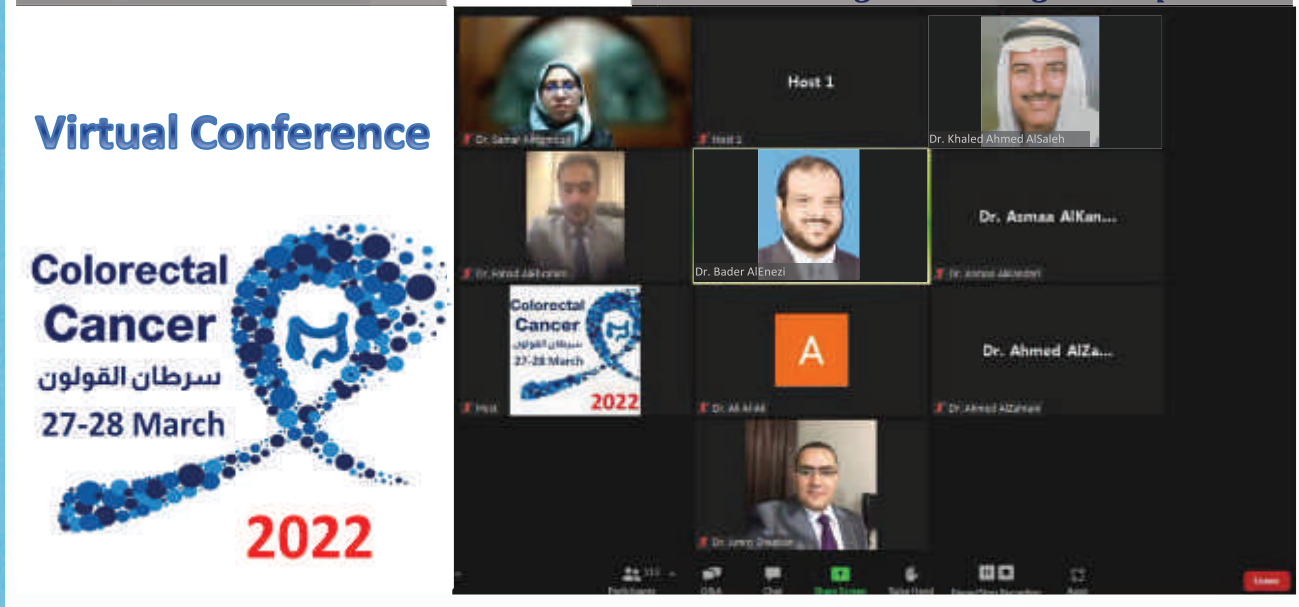

The Official Journal of the Gulf Federation For Cancer Control

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Original Article

Depth of Invasion in Squamous Cell Carcinoma of Buccal Mucosa: Is Magnetic Resonance Imaging a Good Predictor of Pathological Findings?

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Abstract

Introduction or Background: This prospective analysis of patients with squamous cell carcinoma of the buccal mucosa, aimed to analyze the correlation between depth of invasion (DOI) observed in pre–operative imaging and the post–operative histopathological findings, and to assess the predictive value of magnetic resonance imaging.

Patients and Methods: All cases of squamous cell carcinoma of buccal mucosa, planned for primary surgery followed by adjuvant treatment, between June 2017 to December 2019 were included in the analysis. All patients were taken up for imaging using 3 Tesla MR imaging system and subsequently had undergone surgery. The imaging parameters and the histopathological data were analyzed statistically.

Results: Of the 45 patients analyzed, 86.7% were males. Mean age at presentation was 60.62 years. All had squamous histology, with 62.2% being moderately differentiated. 68.9% were T4, 46.7%, N0 and 31.3%, N3. Six node positive patients showed perinodal invasion on histopathology. The mean DOI observed in MRI was 16.54mm, while that in histopathological evaluation was 20.24mm.

Discussion: A significant correlation was observed between imaging and histopathology values in terms of the DOI, with Spearman's Rho correlation coefficient showing **0.693 (p–<0.001)**. Nodal positivity observed in the imaging and the histopathological findings showed only a moderate correlation of **0.409**, with p values of **0.005** (Pearson, Spearman's rho) and **0.007** (Kendall's tau_b). A significant correlation **was not observed** between nodal involvement and DOI assessed by imaging nor with histopathological assessment. With a cut–off value of 5mm as imaging DOI, the positive predictive value (PPV) for nodal positivity was only 37.14%, while the negative predictive value (NPV) was 95%. The sensitivity was 96.3%, and specificity 30.16%. When the cutoff was raised to 10mm, the values for PPV, NPV, sensitivity and specificity were, 44.07%, 61.29%, 68.42% and 36.54%.

Conclusion: Despite being a histopathological parameter, accurate or near accurate evaluation of DOI can be achieved using MR imaging. Our study convincingly shows that magnetic resonance imaging can be considered the imaging of choice for the evaluation of depth of invasion of the tumour in squamous cell carcinoma of the buccal mucosa, though it fails to show any predictive value for nodal involvement.

Keywords: MRI, Squamous cell carcinoma of buccal mucosa, Depth of tumour invasion, Histopathology.

Introduction

Cancers of lip and oral cavity is one of the major causes of death world over, as shown by Globacon 2020 statistics, with a mortality rate of 1,77,757 in both sexes and all ages, with an incidence of 3,77,713 new cases, in both sexes. The highest incidence is documented in Papua New Guinea, Pakistan and India[(1)]. It is a major cause of death in the Indian subcontinent, accounting for 72,616 deaths, and 16.1% of cancers in men and 10.4% among women, with 92,011 and 1,19,992 new

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cases in men and women respectively[2]. Almost 80%–90% of these are directly attributed to tobacco chewing, most often in combination with lime and betel–nut, and to ethanol consumption.(NCRP) The five–year survival drops to a dismal 27% with advanced disease, while the early stages have an impressive 82%[2]. Early detection, meticulous staging and comprehensive treatment hence carries immense importance in these patients.

Anatomically oral cavity has multiple sub–sites, each of which are an entity by itself, and buccal mucosa is one among these. Staging of head and neck cancers, as in most other sites, is based on TNM staging by the American Joint Committee on Cancer (AJCC). Clinical evaluation and staging of a malignancy carry paramount importance, being the basis of the decision on primary treatment. For those cancers where primary treatment is surgical, as in oral cavity tumours, there has been robust evidence from clinical and pathological data in the recent years, which resulted in a separate clinical and pathological TNM staging for this group of tumours in the 8th edition of AJCC, as opposed to the earlier versions[3]. The 8th edition of AJCC staging published in 2017, has thus incorporated depth of invasion (DOI) of tumour and extra nodal extension in the nodes as important parameters deciding the stage of malignancy, apart from tumour dimensions and nodal status[3]. As per this, a tumour size of ≤2cm with a DOI of ≤5mm defines a T1 lesion, a tumour size ≤2cm with DOI of >5mm and ≤10mm or tumour size >2cm but ≤4cm with DOI ≤10mm defines a T2. A tumour >4cm or any tumour with a DOI of >10mm becomes a T3 lesion[3]. Similarly, extra nodal extension (ENE) in any node changes the nodal stage to N3b[3]. This points to the significance of DOI as well as ENE in tumours of buccal mucosa, and as is evident both these are histopathological parameters.

Imaging has always complemented clinical evaluation, especially so in head and neck malignancies. From the discovery of x–rays by Roentgen in late 1895, imaging has evolved from radiographs, dental–radiographs, and panoramic radiographs, through ultrasonogram, to computerized axial tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT) and hybrid methods like PET/CT, PET/MRI and SPECT/CT.

A CT scan, the most ubiquitous imaging modality used, detects the extent of primary tumour, with a sensitivity of 41%–82%, and specificity of 82%–100%. It has a sensitivity of 63%–80%, in assessing bone infiltration, and specificity of 81%–100%[4]. CT can exclude lymph nodal involvement with a sensitivity of 74% and specificity of 85%. MRI, on the other hand, is superior in delineating bone, bone–marrow and soft tissue involvement, the sensitivity being 82% and specificity 66.7%[4]. MRI differentiates the metastatic involvement of lymph nodes with a sensitivity of 51%–74%, and specificity of 95%–100%.

Correlation between imaging and histopathological findings of the oral cavity tumours have been looked into by different authors who have opined the benefits of a pre–treatment accurate evaluation. Goel and colleagues have documented the accuracy of depth of invasion predicted by MR imaging in squamous cell carcinoma of oral cavity,[5] and the predictor value in cervical lymph nodal metastasis, though their study included both oral tongue and gingivo–buccal sulcus tumours.

It is understood that tumour thickness and depth of invasion (DOI) are not synonymous, and the latter is not clinically appreciated accurately, and for every increase in DOI by 5mm the cTNM and pTNM moves up by one level[3]. DOI is measured from the basement membrane level of the normal mucosa closest to the lesion, and a "plumb line" in some instances[3].

Aim

This prospective analysis done in a tertiary cancer care centre, focused on patients with squamous cell carcinoma of the buccal mucosa. The study aimed to analyze the correlation, if any, between the depth of invasion observed in the pre–operative imaging and the post–operative histopathological findings, namely, depth of invasion, T status, node positivity and extra nodal extension, and to assess the predictor value of magnetic resonance imaging.

Materials and methods

All consecutive, biopsy proved cases of squamous cell carcinoma of buccal mucosa, seen in this tertiary cancer care centre, and planned for primary surgery followed by adjuvant treatment, between June 2017 to December 2019 were included in the analysis. Exclusion criteria included patients with inoperable lesions, medical contra–indications, treated with neo–adjuvant chemotherapy, planned for palliative options, metastatic or recurrent disease, unwilling for surgical options, and those treated earlier with surgery, or radiation for head and neck malignancies. Of the 51 cases of carcinoma buccal mucosa registered in this 31–month period, 45 were included in the analysis: four patients had their imaging done from elsewhere, and two patients opted to have their treatment from other centers, and hence were excluded (Fig 1).

After initial biopsy confirmation, all patients were clinically evaluated and counseled, and were taken up for imaging using 3 Tesla (Tesla–unit of magnetic flux density) MR imaging system (GE). A 32–channel head

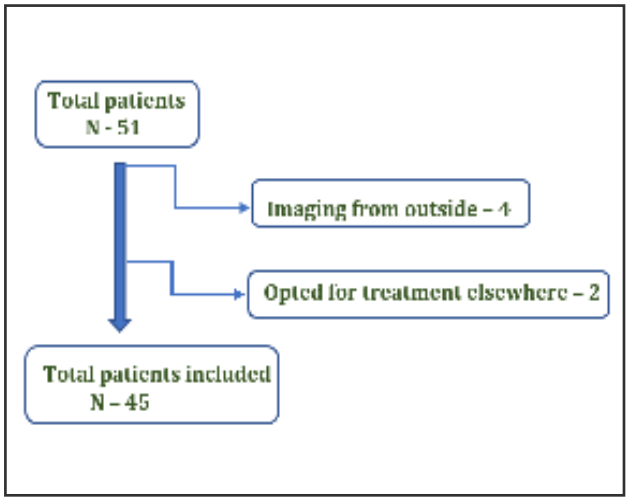

Figure 1: Flow chart of patient accrual

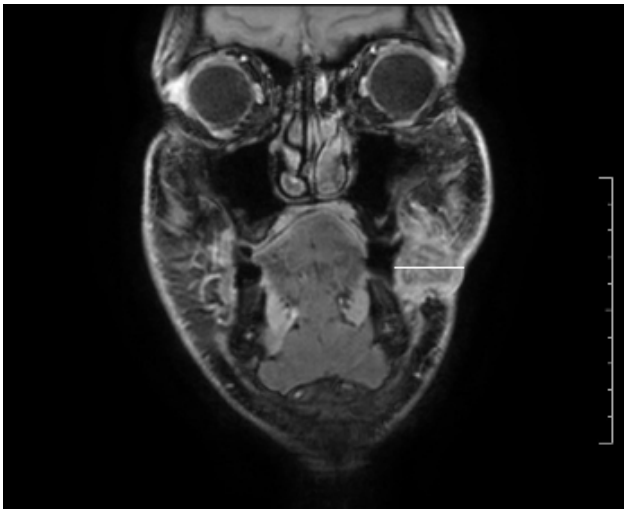

Figure 2: Post–contrast T1 image showing thickening of buccal mucosa on the right side

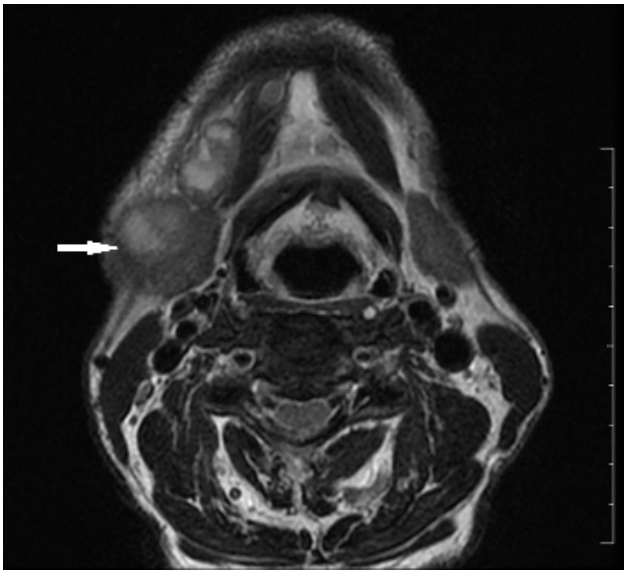

Figure 3: T2 weighted image showing right level 1b node with haziness in the perinodal fat and poor fat plane with submandibular gland

and neck coil was used. Ample time was given, for the inflammatory changes following biopsy to subside, prior to imaging. The timing of the imaging was adjusted to fit in as nearer to the surgical procedure, usually less than a week, so as to reduce the fallacies to a minimum. Volume of coverage for the scan was from skull base to sternal notch with maximum care to include the entire primary tumor and nodal stations. The sequences used were, Cube T1 weighted spin echo, with short TE (Echo Time)/ TR (Repetition Time) with 4 mm thickness and no inter–slice gap in coronal plane, T2 with long TE/TR (85/5339 msec) with 4 mm slice thickness and no inter–slice gap in axial, sagittal and coronal planes, and STIR (Short Tau Inversion Recovery, Short TI – Inversion Time – Inversion Recovery) sequences (TE–42, TR–8723, T1–200 msec), in coronal plane. Post–contrast images were acquired in 3–Dimensional T1 weighted sequences with fat suppression (TE–minimum TR–7.2 msec, NEX (number of excitations)–1.0) in axial plane and were reformatted in sagittal and coronal planes. Gadodiamide (Omniscan – GE Healthcare Inc., Princeton, NJ) was injected intravenously at 1.5cc per second to a maximum dose of 10cc followed by a 10mL saline flush at the same rate using mechanical injector. Care was taken to acquire the images immediately on completion of contrast administration.

Image analysis

Tumor is seen as diffuse thickening of the buccal mucosa which shows extension to gingivobuccal sulcus and alveolus. Lesion shows an intermediate signal on T2 weighted images, lower than the buccinator muscle which enhances on post–contrast T1 weighted images. After going through entire series of images, maximum thickness was assessed in post contrast coronal T1 weighted image with fat saturation. Maximum transverse thickness of the lesion is taken as tumor thickness. Images were reviewed by a single radiologist, with more than 10 years' experience in head and neck imaging, for consistency and to avoid bias.

Lymph nodal levels commonly involved in carcinoma of buccal mucosa are levels IB, and II. Level IB includes the submandibular nodes located in the space bounded by, the inner side of the mandible laterally, the digastric muscle medially, the symphysis menti anteriorly and the submandibular gland posteriorly. Level II contains upper jugular nodes located along the upper two third of the internal jugular vein. These nodes lie in the space deep to sternocleidomastoid muscle and internal carotid artery (ICA) and scalene muscle medially. Anteriorly this space extends up to the posterior end of submandibular salivary gland.

Imaging criteria for involvement varies in the different levels of nodal stations. While a long axis measurement ≥15 mm is taken as a sign of involvement in the level IB nodal stations, for nodal stations of levels II and below it is ≥10 mm. Nodes were evaluated for size, necrosis and perinodal spread. Nodal size was measured in the longest axis in the axial plane in T2 weighted images and categorized into any one of the following groups: 0 –10 mm, 11– 20 mm, 21– 30 mm, or ≥31 mm. Largest suspicious nodes were evaluated for perinodal spread. Criteria for perinodal spread were, irregular nodal margins. perinodal fat stranding and involvement of adjacent structures. (Figure 2, 3)

Following initial staging evaluation, all patients had undergone surgery, usually, a wide local excision, with adequate margins, which conventionally is considered as 1cm beyond any palpable disease margin. Neck dissection done was decided based on the primary disease status. The dissected material was appropriately oriented and inked for pathological evaluation. Tumour dimensions were assessed by the dedicated pathology team, and reporting adhered to international norms. The pathological data was extracted from the medical records and was tabulated. Apart from the imaging and pathological details, the demographic data were also extracted from the electronic medical records, and tabulated and analyzed statistically.

Statistical analysis

The data obtained was tabulated and analyzed statistically using the statistical platform, SPSS (Statistical Package for Social Sciences – 20.0). The imaging parameters and the histopathological data were compared using Paired T test and One–sample test. Correlation tools like Pearson's correlation, Kendall's tau–b correlation coefficient and Spearman's Rho correlation coefficient were used for comparison, and Levene's test for equality of variances was also used. Other tests like chi–square test, Mann–Whitney and other tests were also used.

Results

Of the 51 cases of carcinoma of the buccal mucosa available for evaluation in the study period, 45 were eligible for analysis, after exclusion. There was a male preponderance with 86.7%. Mean age at presentation was 60.62 years (range: 38–83). All patients had squamous histology, with 62.2% having a moderate differentiation. The demographic data and tumor characteristics are presented in **table 1.**

Majority of the patients were having T4 status (68.9%). Of the 45 patients, 21 (46.7%) were node negative histopathologically, and 31.3% were of N3 status. Among the node positive patients only six (6/25–24%; 6/45–13.3%) showed perinodal invasion as per histopathological observation.

The mean depth of invasion observed in the magnetic resonance imaging was 16.54mm, while that in histopathological evaluation was 20.24mm. A significant correlation was observed between the two, namely, imaging and histopathology values in terms of the depth of invasion, with Spearman's Rho correlation coefficient showing **0.693 (p–<0.001)**, Kendall's tau_b

Number	Character	Variable	Number	Percentage
n – 45				
Histology: Squamous cell carcinoma				
1	Age	Mean – 60.2 Years; Range – 38 – 83		
2	Gender	Male	39	86.7
		Female	6	13.3
3	Differentiation	Well	12	26.7
		Moderate	28	62.2
		Poor	5	11.1
4	HPR – T Status	T1	6	13.3
		T2	3	6.7
		T3	5	11.1
		T4	31	68.9
5	HPR – Nodal Status	N0	21	46.7
		N1	4	8.9
		N2	6	13.3
		N3	14	31.1
6	Perinodal spread	No	39	86.7
		Yes	6	13.3

Table 1: General characteristics

	Imaging	Histopathology
Mean	16.54	20.24
Median	15.0	17.0
Range	2–34	2–65

Table 2: Depth of Invasion – Imaging vs Histopathology

Nodal Levels	Imaging	Histopathology
No Nodes	10 (22.2%)	21 (46.7%)
Level I	32 (71.1 %)	20 (44.4%
Level II	16 (35.6%)	15 (33.3%)
Level III	1 (2.2%)	5 (11.1%)
Level IV	1 (2.2%)	2 (4.4%)
Level V	0 (0%)	1 (2.2%)

Table 3: Nodal positivity – Imaging vs Histopathology

correlation coefficient showing **0.550 (p–<0.001)**, and Pearson correlation showing **0.547 (p–<0.001)**. All three had significance at 0.01 level (2–tailed). Paired sample correlation showed a significant correlation between the two (0.547, p–<0.001). The paired sample test also showed a significant p value of 0.040. The details are shown in **Tables 2 and 4.** The Levene's Test for equality of variances as well showed a significance of **0.006** between the two. ANOVA also showed a significance of **0.001** with the measure of association showing an impressive Eta squared value of **0.782**.

The depth of invasion of the tumour as measured in imaging was significantly related to the histopathological T status, as well. Pearson correlation showed a value of **0.585 (p–<0.001)**. and showed significance at 0.01 level (2–tailed). Independent sample test also showed a significant association between the imaging depth of invasion and T status (p–<0.001). **(Table 4)**

Correlations – DOI Imaging vs DOI Histopathology			
		DOI – Imaging – mm	**DOI – HPR – mm**
Pearson Correlation	DOI – Imaging – mm	1	.547(**)
			.000
	DOI – HPR – mm	.547(**)	1
		.000	
Kendall's tau_b Correlation Coefficient	DOI – Imaging – mm	1.000	.550(**)
		.	.000
	DOI – HPR – mm	.550(**)	1.000
		.000	.
		45	45
Spearman's rho Correlation Coefficient	DOI – Imaging – mm	1.000	.693(**)
		.	.000
	DOI – HPR – mm	.693(**)	1.000
		.000	.

Correlations – DOI Imaging vs T Status			
		DOI – Imaging – mm	**pT (HPR): T1 – 1, T2 – 2, T3 – 3, T4 – 4,**
Pearson Correlations	DOI – Imaging – mm	1	.585(**)
			.000
	pT (HPR): T1 – 1, T2 – 2, T3 – 3, T4 – 4,	.585(**)	1
		.000	
Kendall's tau_b Correlation Coefficient	DOI – Imaging – mm	1.000	.463(**)
		.	.000
	pT (HPR): T1 – 1, T2 – 2, T3 – 3, T4 – 4,	.463(**)	1.000
		.000	.
Spearman's rho Correlation Coefficient	DOI – Imaging – mm	1.000	.563(**)
		.	.000
	pT (HPR): T1 – 1, T2 – 2, T3 – 3, T4 – 4,	.563(**)	1.000
		.000	.

Table 4: Correlations – DOI Imaging vs DOI Histopathology, and T Status

**Correlation is significant at the 0.01 level (2–tailed).

		Nodes – HPR Involved –Yes	Nodes – Imaging
Pearson Correlations	Nodes – HPR Involved –Yes	1	.409(**)
			.005
	Nodes – Imaging	.409(**)	1
		.005	
Kendall's tau_b Correlation Coefficient	Nodes – HPR Involved –Yes	1.000	.409(**)
		.	.007
	Nodes – Imaging	.409(**)	1.000
		.007	.
Spearman's rho Correlation Coefficient	Nodes – HPR Involved –Yes	1.000	.409(**)
		.	.005
	Nodes – Imaging	.409(**)	1.000
		.005	.

Table 5: Correlations – Nodal status – Imaging vs HPR
**Correlation is significant at the 0.01 level (2–tailed).

Nodal positivity observed in the imaging and the histopathological findings showed moderate correlation of **0.409** in Pearson, Spearman's rho correlation coefficient and Kendall's tau_b correlation coefficient with p values of **0.005, 0.005 and 0.007** respectively. The paired sample test was also significant between the imaging and HPR findings (p–0.011). **(Table 3 and 5)**

A significance between the imaging DOI and nodal positivity with a **p value of < 0.001** was observed in one–sample test. But a significant correlation **was not seen** between the nodal involvement and DOI assessed by imaging (**Pearson correlation: 0.118, p–0.442,**); nor with histopathological assessment (**Pearson correlation: 0.103, p–0.500**). With a cut–off value of 5mm as imaging DOI, the positive predictive value (PPV) for nodal positivity was only 37.14%, while the negative predictive value (NPV) was 95%. The sensitivity was 96.3%, and specificity 30.16%. When the cutoff was raised to 10mm, the values for PPV, NPV, sensitivity and specificity were, 44.07%, 61.29%, 68.42% and 36.54%.

No significant correlation was obtained between the imaging parameters and the histopathological peri–nodal involvement, either.

Discussion

Squamous cell carcinoma of the buccal mucosa has an aggressive biology, and as shown by Lin and colleagues has high loco–regional recurrence; 57% in their cohort[6]. They had also observed a 41% locoregional recurrence rate in their early T1–T2N0 patients, after single modality treatment[6]. In a retrospective cohort of 207 patients of cancer of the gingivo–buccal complex reported by Walvekar et al, with a median follow up period of 2.85 years, loco–regional failures were 43%, with 80% of the recurrences happening in the first 24 months[7]. Locoregional failure resulted in a dismal mean survival of 9.6 months. They also observed that pre–treatment staging often needed to be upstaged due to histopathological findings of occult nodal metastases[7]. Similar observations were reported from institutions like MD Anderson[8] and by other authors[9].

One of the theories put forth explains that, once the buccinator muscle has been violated by the malignancy, there is no anatomical barrier to contain the lesion, and it spreads into the buccal fat space, which contains the buccal pad of fat, the Stenson's duct, facial nerve branches, facial blood vessels and lymphatics and lymph nodes as well as the accessory parotid gland. It is a space bound by buccinator muscle medially, superficial layer of deep cervical fascia and skin laterally, orbicularis oris muscle anteriorly and masseter muscle posteriorly[10].

A diligent pre–treatment evaluation of the lesion thus carries immense importance for accurate staging and deciding on the treatment options. As in most solid tumours, AJCC staging is used for staging of buccal mucosal malignancies. With the incorporation of DOI as a decisive parameter in the staging of these tumours, accurate assessment of this has become a vital factor in the pre–treatment evaluation. An ideal imaging modality should be one which can predict the stage as close to the histopathological observations.

Magnetic resonance imaging has evolved as one of the most useful and accurate pre–operative evaluation

tools in the management of head and neck malignancies, because of the excellent soft tissue contrast observed, which helps in differentiating tumour from adjacent normal structures accurately[11]. MRI thus is a superior and optimal imaging option for staging the primary[12]. Nodal staging, on the other hand, still remains elusive, with all imaging modalities being equivalent, and falling short of the surgical staging[12]. Patel et al had observed that among the nodal stations, level I had the highest risk of metastases (50%), followed by levels II (28.6%), III (11.9%), IV (7.14%) and V (2.38%).

In our cohort of 45 patients with squamous cell carcinoma of buccal mucosa, we observed a significant correlation between the DOI observed through imaging and the final histopathological finding, as shown by the Spearman's Rho (0.712; p–<0.001), and other tests. The imaging DOI was found to significantly correlate with the pathological T status as well. Singh and colleagues had also observed a good correlation between the imaging parameters like tumour depth and width, and, though their cohort had 50 patients, buccal mucosal patients were only nine[14]. Moreover, their analysis was prior to AJCC 8th revision, and did not stress on the DOI. We have also observed that MR imaging is significantly concordant with histopathological dimensions in squamous cell carcinoma of other subsites of oral cavity[15].

A prospective analysis of the accuracy of detecting a lymph nodal metastasis by an imaging modality, as compared to histopathological findings was done by Stuckensen et al from Germany in 2000. They reported a sensitivity, specificity and accuracy of 70%, **82%** and 75% for PET, **84%**, 68% and 76% for Ultrasonogram, 66%, 74% and 70% for CT, and 64%, 69% and 66% for MRI[16]. They had concluded that PET had the highest specificity and ultrasonogram scored above others in sensitivity. A diffusion weighted MR imaging was also found to be less useful in determining a positive node by Wendl and colleagues, due to limited sensitivity and specificity[17].

Our analysis to elucidate a correlation between the DOI and histopathological nodal positivity was also futile. No significant correlation between the DOI and nodal positivity was observed. We observed a negative predictive value (NPV) of 95% with a DOI cutoff of 5 mm, while the same came down to 61.29% for nodal positivity with a DOI of 10mm. Similarly, we also failed to observe any correlation between the imaging parameters and perinodal spread observed histopathologically. A recent study by Lowe et al have quoted a good NPV for [^{18}F] Fluorodeoxyglucose Positron Emission Tomography/ Computed Tomography in head and neck squamous cell carcinoma[18]. A similar observation was made by Yen et al in 2005, where they observed from their cohort of 114 patients of buccal mucosa squamous cell carcinoma, that, though both MRI and CT were equivalent in characterizing the tumour dimensions, nodal predictivity was better with PET imaging[19].

Conclusion

Accurate prediction of tumour size is mandatory for comprehensive treatment planning. Despite being a histopathological parameter, accurate or near accurate evaluation of depth of invasion can be achieved using MR imaging, and since it is a decisive factor in tumour staging, this helps in pre–treatment staging to a great extent. Thus, our study convincingly shows that magnetic resonance imaging can be considered the imaging of choice for the evaluation of depth of invasion of the tumour in squamous cell carcinoma of the buccal mucosa, though it fails to show any predictive value for nodal involvement.

Ethical statement

Patients were accrued after obtaining clearance from Institutional Scientific Review Board and from Institutional Ethical Committee. Signed informed consent forms were obtained from all patients prior to treatment as an institutional policy, with approval for scientific usage of data.

Declaration of Conflict of interests

None of the authors have any conflict of interests to declare.

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