Original Article

Sensitivity and Specificity of Magnetic Resonance Imaging in Prediction of Cervical Lymph Node Metastasis in Oral Squamous Cell Carcinomas

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Abstract

Background: The inaccuracies in clinical examination have been well-documented while advanced imaging modalities including computed tomography (CT) and magnetic resonance imaging (MRI) have been shown to have superior diagnostic accuracy in detecting occult and nodal metastasis. The aim of the present study was to identify as well as evaluate the inaccuracies in clinical examination and of clinical diagnostic criteria in known cases of oral squamous cell carcinomas (OSCCs) with the help of MRI.

Methodology: A total of 24 patients attending as outpatients were included in the study while clinically diagnosed and histopathologically proven cases of OSCC were examined clinically and then, subjected to advanced imaging with the help of MRI. Statistical Analysis Used: Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 17.0 (SPSS Inc., Chicago, IL, USA) while paired t-test was performed for evaluating size of tumor and lymph node recorded on clinical and imaging findings. $p<0.05$ was considered statistically significant.

Results: Detection of tumor size and lymph node metastasis were found to be higher in case of MRI than when accomplished by clinical staging alone while paired t-test values for difference in results were found to be statistically significant ($p<0.05$).

Conclusions: The present study showed that clinical diagnostic criteria alone were not sufficient and reliable for detecting metastatic lymphadenopathy highlighting the significance of advanced imaging modalities like MRI for an efficient pre-operative diagnostic work-up as well as, as a tool for planning treatment in patients with OSCCs.

Key words: Magnetic Resonance Imaging; Metastasis; Multimodal Imaging; Oral Squamous Cell Carcinoma

Introduction

Oral squamous cell carcinomas (OSCCs) are sixth most common cause of cancer-related deaths worldwide.[1] In the Indian scenario, oral cancer is the

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second most common cancer related to deaths.[2] The presence of metastatic cervical lymphadenopathy is of particular importance as with every single nodal metastasis, survival of the patient is reduced by half.[3] Thus, regional metastasis is one of the most important factors in deciding for prognosis and planning treatment in patients with OSCCs.[4-6] The inaccuracies in clinical examination have, also, been well-documented while advanced imaging modalities including computed tomography (CT) and magnetic resonance imaging (MRI) have been shown to have superior diagnostic accuracy in detecting occult and nodal metastasis.[7-11] Most commonly used, tumor (T), node (N) and metastasis (M) classification (TNM classification) system fails to define the exact size and measurements of tumor including diameter, length, width, area, volume and tumor thickness and clinical issues related to it.[12-14] An appropriate management of OSCC cases requires a thorough understanding of factors affecting incidence, patterns and prognostic implications of nodal metastasis.[6] Identification of such prognostic factors could constitute one of the important keys to reduce mortality, morbidity and most importantly, the recurrences in treated patients. The prognosis of patients with OSCCs that are treated early, in initial phases of malignancy, is found to be better because cure is achieved with less complex and lesser aggressive measures than what is obtainable in case of lesions that have reached advanced stages or, metastases. Despite higher incidence and also, higher mortality rates reported from India, no study describing diagnostic accuracy of important prognostic factors like tumor thickness related to lymph node metastasis using modern imaging techniques as well as inaccuracies in clinical examination have been documented.[2,15] Furthermore, a number of studies have identified that among all aspects of tumor size studied, tumor thickness can be an important indicator in prediction of nodal metastasis as well as local recurrences and survival in patients with OSCC.[16-23] Several such studies have been conducted on post-operative, resected specimens while there are very few studies reported which were conducted pre-operatively. Further complicating this situation is the observation that tumor size involving different areas has been found to affect different levels of lymph nodes and thereby, controls survival in a varied manner.[4,5] Hence, an accurate pre-operative assessment of tumor size, in its all possible dimensions, becomes an essential component in optimizing treatment algorithm.[24] Magnetic resonance imaging (MRI) is a powerful imaging tool for cross-sectional analysis of head and neck. This is, especially, true with regards to oro-pharyngeal neoplasms wherein soft tissue spread, nodal disease, peri-neural invasions and osseous involvement significantly alter treatment plan and prognosis.[24,25] The aim of the present study was to identify as well as evaluate the inaccuracies in clinical examination and of clinical diagnostic criteria in known cases of oral squamous cell carcinomas (OSCCs) with the help of MRI.

Materials and Methods

A total of 24 patients including 11 patients with OSCC involving alveolus, 6 patients with OSCC involving tongue and 7 patients with OSCC involving buccal mucosa attending as outpatients were included in the study while clinically diagnosed and histopathologically proven cases of OSCC were examined clinically and then, subjected to advanced imaging with the help of MRI. Patients with known systemic diseases, those who had received any previous treatment in the form of radiotherapy, surgery or, chemotherapy, those with known contraindications to MRI including patients with cardiac pacemaker, cochlear implants, ocular and dental implants and patients in whom Gadolinium-based contrast agents were contraindicated, were excluded. The study protocol was approved by the Institutional Ethics Committee while a written, informed consent was obtained from all patients who participated in study. All patients were, then, subjected to routine blood investigations, fine needle aspiration cytology (FNAC) of ipsilateral submandibular lymph node (Level I) and incisional biopsy of oral lesion to confirm the diagnosis. As part of pre-diagnostic work-up, a thorough clinical examination was performed while details were recorded in a specially devised proforma. Complete lymph nodal examination was carried-out. The armamentarium used for MRI examination included 1.5 Tesla Magnetom Avanto Systems (Siemens, Germany). All patients were asked to fast for 6 hours prior to MRI examination while specific sequences were obtained including axial T1-weighted, spin-echo images from face and neck region including maxilla and mandible wherein localizer was widened in cases of larger fields (TR/TE: 400-640 ms/10-14 ms; slice thickness: 4-7 mm; gap: 1-2 mm; field of view: 24-38 cm; NEX: 1-2; matrix: 256 x 192-256). Followed by this, axial T2-weighted, fast spin-echo images of face and neck (TR/TE: 4000-6000 ms/90-110 ms; echo-train length: 8; slice thickness: 4-7 mm; gap: 1-2 mm; field of view: 24-38 cm; NEX: 2; matrix: 512 x 256), sagittal T2-weighted, fast spin-echo images from cantho-meatal line to supra-clavicular level (TR/TE:

4000-6000 ms/90-110 ms; echo-train length: 8; slice thickness: 4-7 mm; gap: 1-2 mm; field of view: 24-32 cm, NEX: 2; matrix: 512 x 256) and unenhanced and enhanced fat-suppressed, coronal T1-weighted images (TR/TE: 126 ms/2.47 ms; flip angle: 70°; slice thickness: 4-7 mm; gap: 1-2 mm; field of view 30-36 cm; NEX: 2-4; matrix: 256 x 192-256; spectral fat suppression) were obtained. Contrast-enhanced images were obtained after intra-venous (i.v.) injection of 0.1 mmol/kg body weight of Gadobenate dimeglumine (Multihance; Bracco, Milan, Italy). Post-contrast images were obtained in two planes. Additional sequences were, also, taken in few patients as per requirement while doing procedure. With the help of these sequences, tumor size was assessed in terms of diameter, length, width, area, volume and tumor thickness while cervical lymph nodes were assessed in terms of their size, number and grouping or, confluence and associated changes, if any. MRI parameters were analyzed by expert radiologists who were blinded to clinical findings. Tumor size in all three dimensions was assessed for its relation with lymph node metastasis. For measuring tumor thickness, a horizontal line joining two tumor-mucosa junctions was drawn as reference line and tumor thickness was measured by drawing perpendicular lines from said reference line to the point of maximal tumor projection and invasion as seen on MRI images and calculated as the greatest determined tumor thickness by adding these two parameters. The diagnosis of lymph node metastasis was made based on specific imaging criteria on MRI including a size >8 mm and round shape. Size criterion was taken as standard and diagnostic reliability of all other criteria were calculated for predicting lymph node metastasis. All patients were assessed for tumor size, lymph node metastasis, lymph nodal grouping and peri-neural spread of tumor using MRI while diagnostic reliability for lymph node metastasis in relation to tumor thickness was calculated. The results obtained were, then, subjected to statistical analysis while values for sensitivity, specificity, positive and negative predictive values and accuracy were calculated.

Statistical Analysis Used: Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 17.0 (SPSS Inc., Chicago, IL, USA) while paired t-test was performed for evaluating size of tumor and lymph node recorded on clinical and imaging findings. $p<0.05$ was considered statistically significant.

Results

The age of patients in the study ranged from 37-84 years with a mean age of 60 years. The distribution of cases according to age and gender is shown in Table 1 while by site, tumor differentiation and FNAC positive lymph nodes in Table 2. Out of the 24 patients included in study with palpable lymph nodes, 20 lymph nodes were found positive for FNAC confirming metastatic spread. (Table 2) Table 3 reveals the distribution of cases by clinical and imaging staging wherein it was observed that 5 cases were upgraded from T2 to T3, 2 from T3 to T4 while only one patient was downgraded from T2 to T1 on MRI examination. On evaluating lymph nodes, 5 cases (20.83%) were upgraded from N0 to N1 while one case (4.17%) was upgraded from N2a to N2b as observed on MRI. Table 4 reveals relationship between tumor thickness and lymph node metastasis for all levels of lymph nodes wherein tumor thickness observed in present study varied from 1.4 to 5.6 cm while positive cases for lymph node metastasis were found to be more when tumor thickness was >3 cm in case of both Level I (88.89%) and all levels (81.25%) of lymph nodes with the corresponding values being statistically significant ($p<0.05$). Table 5 shows the diagnostic reliability of different cut-off thickness in relation to lymph node metastasis for all levels of lymph nodes wherein the diagnostic accuracy for detection of lymph nodal metastasis in relation to tumor thickness of 2 cm, 3 cm and 4 cm was reported to be 40.0%, 32.0% and 76.0% respectively for Level I and 36.96%, 41.30% and 69.57% for all levels of lymph nodes. Table 6 shows relationship between lymph node number and metastasis while Table 7 shows the diagnostic reliability for lymph node metastasis in relation to lymph node number, grouping and associated changes for all levels of lymph nodes. The diagnostic accuracy for lymph node metastasis in relation to lymph node number, grouping and associated changes was found to be 56.0%, 56.0% and 52.0% respectively for Level I while 60.87%, 58.7% and 50.0% for all levels of lymph nodes. Table 8 shows comparison of clinical and imaging staging with varied tumor-related parameters and lymph node size (in mm) wherein on analysis, it was found that tumor sizes identified on imaging with a mean of 4.04 mm for length and 3.08 mm for width respectively were significantly higher than as assessed by clinical staging with a mean of 2.94 mm and 2.47 mm for length and width respectively. Similarly, sizes of lymph nodes identified on imaging with a mean of 11.45 mm was found to be higher than as assessed by clinical staging with a mean of 8.00 mm with the corresponding values being statistically significant ($p<0.05$). Table 9 reveals overall diagnostic reliability of MRI staging for lymph node metastasis wherein it could be observed that the overall specificity, sensitivity and positive and negative predictive values as observed on imaging were found to be 100.0%, 75.0%, 72.73% and 100.0% respectively while overall accuracy achieved was 85.0%.

Table 1: Distribution of cases by personal characters

Personal characteristics	n	%
Age (in years)		
Up to 50	6	25.0
51-65	10	41.7
Above 65	8	33.3
Sex		
Male	15	62.5
Female	9	37.5
Total	24	100.0

Table 2: Distribution of cases by site, tumor differentiation and FNAC positive lymph nodes

Variable	n	%
Site		
Alveolus	11	45.8
Tongue	6	25.0
Buccal mucosa	7	29.2
Total	24	100
Tumor differentiation		
Poor	2	8.3
Moderate	7	29.2
Well	15	62.5
Total	24	100.0
FNAC positive lymph nodes		
Positive	20	83.33
Negative	4	16.67
Total	24	100.0

Table 3: Distribution of cases by clinical and imaging staging

Stage	Clinical		Imaging	
	n	%	n	%
T1N1M0	1	4.2	2	8.3
T2N0M0	2	8.3	1	4.2
T2N1M0	14	58.3	9	37.5
T3N1M0	7	29.2	9	37.5
T4N1M0	-	-	3	12.5
Total	24	100.0	24	100.0

Table 4: Relationship between tumor thickness and lymph node metastasis for all levels of lymph nodes

Levels	Tumor Thickness (cm)	Lymph Node Metastasis		Total	%	Chi-square value	p-value
		Negative	Positive				
Level I	Up to 2	4	2	6	33.33	7.6830	0.0210*
	2-3	7	3	10	30.0		
	>3	1	8	9	88.89		
	Total	12	13	25	52.0		
All levels	Up to 2	8	3	11	27.27	8.9260	0.0120*
	2-3	11	8	19	42.11		
	>3	3	13	16	81.25		
	Total	22	24	46	52.17		

*p<0.05- statistically significant

Table 5: Diagnostic reliability of different cut-off thickness in relation to lymph node metastasis for all levels of lymph nodes

Levels	Tumor Thickness (cm)	Specificity (%)	Sensitivity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Accuracy (%)
Level I	2	66.67	15.38	42.11	33.33	40.00
	3	41.67	23.08	33.33	30.00	32.00
	4	91.67	61.54	68.75	88.89	76.00
All levels	2	63.64	12.50	40.00	27.27	36.96
	3	50.00	33.33	40.74	42.11	41.30
	4	86.36	54.17	63.33	81.25	69.57

Table 6: Relationship between lymph node number and metastasis

No. of lymph nodes enlarged	Lymph Node Metastasis				Total
	Negative	%	Positive	%	
1	17	56.67	13	43.33	30
2	4	36.36	7	63.64	11
3	0	0.00	1	100.00	1
4	1	50.00	1	50.00	2
5	0	0.00	1	100.00	1
6	0	0.00	1	100.00	1
Total	22	47.83	24	52.17	46
Chi-square value=3.0701, p-value=0.2152					

Table 7: Diagnostic reliability for lymph node metastasis in relation to lymph node number, grouping and associated changes for all levels of lymph nodes

Levels	Lymph Node	Specificity (%)	Sensitivity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Accuracy (%)
Level I	Number	75.00	38.46	52.94	62.50	56.00
	Grouping	83.33	30.77	52.63	66.67	56.00
	Associated changes	100.00	7.69	50.00	100.00	52.00
All levels	Number	77.27	45.83	56.67	68.75	60.87
	Grouping	81.82	37.50	54.55	69.23	58.7
	Associated changes	100.00	4.17	48.89	100.00	50.00

Table 8: Comparison of clinical and imaging staging with varied tumor-related parameters and lymph node size (in mm)

Staging	n	Mean	Std. Deviation	Mean Diff.	t-value	p-value
Tumor Length (mm)						
Clinical	24	2.94	1.18	-1.10	-7.22	0.0001*
Imaging	24	4.04	1.71			
Tumor Width (mm)						
Clinical	24	2.47	0.97	-0.61	-3.38	0.0001*
Imaging	24	3.08	1.53			
Lymph node size (mm)						
Clinical	20	8.00	5.48	-3.45	4.21	0.0005*
Imaging	20	11.45	7.22			

*p<0.05- statistically significant

Table 9: Overall diagnostic reliability of MRI staging for lymph node metastasis

Clinical Staging	Imaging Staging		Total (Cut-off)
	Negative	Positive	
Negative	8	3	11
Positive	0	9	9
Total (Metastasis)	8	12	20
Specificity (%)	100.00		
Sensitivity (%)	75.00		
Positive Predictive Value (%)	72.73		
Negative Predictive Value (%)	100.00		
Accuracy (%)	85.00		

Discussion

Although computed tomography (CT) remains the most widely used imaging modality, it delivers a very high dose of radiation to patients while on the contrary, magnetic resonance imaging (MRI) is a safer and new procedure for evaluation of OSCCs and associated lymphadenopathy which is preferred for its excellent soft tissue resolution, especially, in 3D visualizations.[26-28] Ultrasonography (USG), though, also, used for soft tissue imaging, is a highly operator dependent imaging modality.[19] Though MRI is considered to be a costly imaging modality till date, its use for accurate pre-operative evaluation of tumor size and metastatic lymphadenopathy can significantly decrease morbidity in OSCC patients.[29-31]

The use of MRI, in head and neck region, is, also, supported by facts that oro-facial tissues have variable amount of fat in different regions and tumor extent can be clearly seen on MRI images by fat suppression techniques. Moreover, MRI images are free from metal streak artifacts seen on CT images. The major limitations of MRI, though, include its restricted availability and difficulty in performing MRI scan in claustrophobic, old and uncooperative patients. MRI is, also, contraindicated in patients with ferromagnetic-based implants including cardiac pacemakers and aneurysmal bone and vascular clips.[32-35]

Inaccuracies in clinical examination have been well-documented.[36,37] In the present study, tumor size as evaluated by TNM staging based on MRI was found to be higher for most of the cases as compared to that documented on clinical examination. Only one case was downgraded from T2 to T1 on MRI examination, the probable reason for which could be that the largest tumor dimension got obscured within 4-7 mm slice thickness used for acquisition of MRI images. Also, nodal involvement was found to be more when evaluated with MRI as compared to clinical staging wherein 5 cases (20.83%) were upgraded from N0 to N1 while one case (4.17%) was upgraded from N2a to N2b as observed on MRI.

It was, also, evident from findings of present study that whenever tumor sizes were larger, widespread nodal metastases were noticed while a significant difference was noted in tumor sizes as identified on imaging than as assessed by clinical staging. Similarly, sizes of lymph nodes identified on imaging were found to be higher than as assessed by clinical staging with the corresponding values being statistically significant ($p<0.05$). The results of present study revealed the overall specificity, sensitivity and positive and negative predictive values as observed on imaging to be 100.0%, 75.0%, 72.73% and 100.0% respectively while overall accuracy achieved was 85.0%.

Bipat et al[38], after reviewing 57 high quality studies, concluded that sensitivity of MRI was higher (60%) as compared to CT (43%) for detecting metastatic lymph nodal involvements. Hayashi et al[39], though, reported an accuracy of 75% with a cut-off value of 5 mm tumor thickness for subsequent lymph node metastasis when using CT. In the present study, a diagnostic accuracy of 76.0% was achieved with a cut-off value of 4 cm tumor thickness for Level I while 69.57% for all levels of lymph nodes when using MRI. Diagnostic accuracy reported by Hayashi et al[39] using CT and present study using MRI are comparable, however, disadvantages of CT have to be noted.

Significantly increased risk for cervical lymph nodal metastasis was, also, noticed by Fukano et al[17] and O-charoenrat et al[19] with tumor thickness of >5 mm for oral and oro-pharyngeal carcinomas. Furthermore, poor survival and consideration of elective neck treatment was proposed by Brown et al[16] and Urist et al[21] for tumor thickness of >2 mm for OSCCs of tongue and 6 mm for OSCCs of buccal mucosa respectively. It is true that tumor deposits within a node are only microscopic and detection of metastasis by CT or, MRI is impossible at microscopic level, however, when metastases are large enough to be detected by CT or, MRI, criteria are necessary to stage the disease properly.[35]

There are no clear recommendations regarding size criterion and different values have been studied. The present study used size criteria of 8 mm as standard for predicting lymph node metastasis in analyzing accuracy of other imaging criteria. There are very few studies that have considered number of lymph nodes involved as an imaging criterion to predict prognosis in OSCCs, though, literature review reveals worse prognosis whenever more number of lymph nodes were involved in a given carcinoma.[31,40-46] In the present study, diagnostic accuracy for lymph node metastasis in relation to lymph node number, grouping and associated changes was found to be 56.0%, 56.0% and 52.0% respectively for Level I while 60.87%, 58.7% and 50.0% for all levels of lymph nodes.

Furthermore, specificity values of 83.33% and 81.82% were observed in the present study in relation to grouping of lymph nodes as a diagnostic criterion for predicting lymph nodal metastasis, the finding, though, was contradictory to the finding of study conducted by van den Brekel et al[31] who stated that grouping criterion did not increase specificity for detection of lymph node metastasis. Also, in present study, a sensitivity of 4.17-7.69% while a specificity of 100.0% for peri-neural spread as imaging criterion was reported on MRI, though, relatively higher values of sensitivity and specificity were observed in the study conducted by Hanna et al[47] with a reported sensitivity of 100% and specificity of 85% using MRI and 88% and 89% respectively using CT. The low value of sensitivity observed in present study, though, can be attributed to the fact that only one case in present study was found to have associated changes with lymph node metastasis in the form of peri-neural spread on MRI.

Clinical examination remains the worldwide standard and the very first step for initial screening and evaluation of OSCCs, however, it fails to define exact tumor size and extent, and associated lymph nodal metastasis. Also, surface size is the main verifiable clinical parameter available before treatment because nodal spread estimates are often erroneous while biopsies, also, often do not reflect the whole tumor histology.[13,48,49] Furthermore, thickness of tumor or, its volume, even if, assessed before treatment, can only be a rough estimate which are not mentioned in the official TNM manual.[50,51]

In patients with head and neck carcinomas, prognosis is usually obtained based on TNM classification which is based on clinical criteria and is highly useful, especially, to assess the essential features such as local extension, regional dissemination and distant metastasis.[52,53] However, this classification lacks a clear idea about aggressiveness of tumor and inflammatory versus metastatic lymph nodal enlargements. Clinical impression of nodal metastasis on first examination is often overestimated as has been suggested by Sako et al[48] and this might be because of the regional inflammatory reaction to a metastatic node as has been reported by Moore et al[13]. Also, histopathological examination, which is the gold standard, is currently being done post-operatively only. In such circumstances, a study correlating MRI findings and histologic tumor thickness and associated lymph nodal metastasis in the assessment of OSCCs gives a clear view about this aspect. One such study done by Lam et al[20] in oral tongue carcinomas stated that radiologic tumor thickness as measured on contrast-enhanced MRI images had a significant correlation with histologic tumor thickness.

OSCCs may have different behaviors in different areas of oral mucosa. Thus, traditional TNM clinical staging fails to predict exact prognosis. It has, also, been reported previously that when dealing with primary tumors, advanced cases with infiltration of adjacent structures were hardly assessed on clinical examination with the percentage of accuracy found to be higher when CT and MRI were used for classification and staging of tumor as compared to TNM clinical staging alone.[54,55] In the present study, only 40% cases were found to be true positive for detecting lymph nodal metastasis using clinical diagnostic criteria while the numbers were 55% using imaging criteria. Thus, imaging criteria were found to be more accurate than clinical diagnostic criteria. This might, also, be because none of the available imaging criteria for lymph nodal metastasis are standardized till date.

It is of further interest to note that few cases in present study, particularly, tongue and buccal mucosa, showed involvement of Level III and IV lymph nodes on MRI but were clinically occult (N0), thereby, emphasizing the significance of MRI in providing useful information regarding treatment planning in such cases. By detecting some otherwise clinically occult lymphadenopathy, MRI may have increased sensitivity for detecting positive nodes and consequently, may decrease risk of occult metastasis which might be of extreme significance in decision making as treatment strategies for N0 and N1 or, N2 necks differ distinctly.[56-63] The comparatively lower sensitivity and specificity reported in present study might be attributed to the reason that cases involving three different regions of oral cavity were included which might have different patterns of nodal metastasis. Furthermore, OSCCs involving alveolus do not spread to lymph nodes as rapidly as the ones involving tongue and buccal mucosa.[4,5,19,39]

Conclusions

The present study revealed that clinical diagnostic criteria alone were not sufficient and reliable for detecting metastatic lymphadenopathy highlighting the significance of advanced imaging modalities like MRI for an efficient pre-operative diagnostic work-up as well as, as a tool for planning treatment in patients with practically incurable OSCCs. Based on the findings of present study, it was, also, observed that whenever tumor size, particularly, tumor thickness of >4 cm, was observed, cervical lymph nodal metastasis could be predicted accurately which, in turn, had a significant impact on prognosis. The study did encounter a limitation in the form of enhancement of inflamed and edematous soft tissues on MRI, especially, on T2-weighted, spin-echo images, but this was seen as a common drawback in previous studies as well, related to MRI.

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