Oral cancer staging established by magnetic resonance imaging

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Abstract: The aim of this study was to compare clinical staging and magnetic resonance imaging (MRI) staging for oral cancer, and to assess inter-observer agreement between oral and medical radiologists. A total of 10 patients diagnosed with oral cancer were assessed before treatment. A head and neck surgeon performed clinical TNM staging. Two medical radiologists and two oral radiologists performed a new staging assessment by interpreting MRI scans, without prior knowledge of the clinical staging. They evaluated the extent of the primary tumor (T), metastasis to regional lymph nodes (N) and grouping by stages. The data were analyzed using the Kappa Index. There was significant agreement ($p < 0.05$) between the clinical and MRI staging assessments made by one oral radiologist for N stage, and between those made by one medical radiologist for the T and N stages and for the grouping by stages. In the MRI assessment, there was significant agreement among all four observers for both T stage and grouping by stages. For the N stage, there was no significant agreement between one oral radiologist and one medical radiologist or between both medical radiologists. There was significant agreement among the remaining radiologists. There was no agreement between the clinical and MRI staging. These results indicate the importance of using MRI for the diagnosis of oral cancer. Training initiatives and calibration of medical and oral radiologists should be promoted to provide an improved multidisciplinary approach to oral cancer.

Descriptors: Magnetic Resonance Imaging; Mouth Neoplasms; Head and Neck Neoplasms.

Introduction

The prognosis of carcinoma of the maxillofacial region is influenced by a variety of factors, such as the degree of cellular differentiation, size, location, presence of infiltration into the bone tissue, immune response, age, gender, patient's socio-economic status and the presence of cervical lymph node metastasis, the latter being considered the most significant factor when determining the prognosis.[1-3] Incidence and mortality rates vary from one country to another and even within countries, because of differences in customs, especially tobacco use and alcohol consumption, environmental factors and the quality of medical care.[4] Oral cancer is diagnosed after clinical examination, biopsy and anatomic pathology examination of the lesion have been carried out. After the diagnosis has been established, an assessment is then needed of the extent and spread

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of the disease. Staging, which can be defined as the quantification of the clinical parameters of the disease, helps in making therapeutic decisions and in establishing a prognosis for the patient.[1-3,5,6] The TNM system classifies the anatomical extent of the disease in any part of the body, by using clinical observation and histological and surgical complementation, or diagnostic imaging methods.

The choice of appropriate treatment for patients with oral cancer depends largely on accurate pretreatment staging and, above all, on the detection of cervical lymph node involvement.[2,3,7] In cases of clinically negative necks (N0), the clinical examination may present up to a 40% failure rate in detecting lymph node metastases.[2,3,8,9] A combination of clinical and imaging examinations is essential for detecting metastatic lymph nodes and establishing the prognosis.[10,11] Of the imaging modalities, computed tomography (CT) and magnetic resonance imaging (MRI) seem to be the most appropriate for the pre-therapeutic staging of head and neck tumors, because they provide information on the extent of the lesion, infiltration of large vessels and metastases in lymph nodes.[3,12-14]

The major advantage of MRI is that it provides excellent soft tissue detail visualization and does not involve any biological risks for the patient. Research that can facilitate or provide further information on staging means that patients will be adequately treated and consequently have a greater chance of being cured. The aim of this study was to compare the staging (TNM classification) established by clinical and MRI examinations for oral cancer, and to assess inter-observer agreement between medical and oral radiologists when analyzing MRI scans.

Methodology

Sample

A total of 10 patients seen at the Oral Cancer Center at the Division of Dentistry in the University Hospital of Brasília (UnB), from October 2005 to December 2008, with a histologically proven diagnosis of oral squamous cell carcinoma were examined and submitted to MRI before treatment. This study was approved by the Ethics Committee at UnB (no. 025/2007) and informed consent was obtained from all patients. Table 1 presents the clinical characteristics of the patients.

After clinical examination and biopsies, the patients were referred to a head and neck surgeon to establish their clinical TNM stage and undergo treatment. They concomitantly underwent the CT and MRI examinations. The CT data were published in a previous study.[15] Four observers interpreted the MRI scans. Observers 1 and 2 were dental specialists holding a Master's in oral radiology, and Observers 3 and 4 were medical radiologists. These four radiologists established staging based on the MRI scans without any prior knowledge of the clinical staging already established by the head and

Table 1 - Demographic and clinical data of patients in the study sample.

Case	Gender	Age	Tobacco use	Alcohol consumption	Primary site – Side	Clinical TNM	Grouping
1	Female	50	No	No	Gum – R	T2N0M0	II
2	Male	72	Yes	Yes	Base of tongue – L	T3N0M0	III
3	Male	55	Yes	Yes	Retromolar region – L	T2N1M0	III
4	Male	51	Yes	Yes	Floor of mouth – R/L	T4N2M0	IVA
5	Male	41	Yes	Yes	Tongue – R/L	T4N2M0	IVA
6	Male	69	Yes	Yes	Floor of mouth – R/L	T4N0M0	IVA
7	Female	48	Yes	Yes	Side of tongue – R	T1N0M0	I
8	Female	50	Yes	No	Base of tongue – R	T1N0M0	I
9	Male	62	Yes	Yes	Side of tongue – R	T1N0M0	I
10	Male	54	Yes	Yes	Floor of mouth – R	T2N2M0	IVA

R = right; L = left.

neck surgeon.

Three parameters were evaluated, namely, the extent of the primary tumor (T), the presence/absence and extent of metastasis in regional lymph nodes (N) and the grouping by stages. The criteria established by Prehn *et al.*[16] were used to ascertain which cervical lymph nodes were affected when cervical metastasis occurred.

Magnetic resonance imaging and interpretation

MRI was performed with a Signa Excite 1.5 high-field device (1.5 Tesla) (General Electric Healthcare Inc., Milwaukee, USA), following the protocol of the institution. Images of the head and neck region were taken to assess cervical lymph node involvement. The examinations included T_1 (TR/TE, 350/13.1 ms; FOV 24 × 24 mm; slice width/gap, 3,5/1 mm; slice number, 30), T_1 with contrast (TR/TE, 300/4.8 ms; FOV 24 × 24 mm; slice width/gap, 3,5/1 mm; slice number, 30) and T_2-weighted (TR/TE, 4600/99.4 ms; FOV 26 × 26 mm; slice width/gap, 5/1 mm; slice number, 30) sequences on three anatomical planes (axial, coronal and sagittal). A gadolinium-based contrast agent (Gd/DTPA - Diethylene Triamine Pentaacetic Acid) was used.

The MRI scans were interpreted on a Toshiba Satellite A65 laptop computer (Toshiba America Information Systems, Inc., Irvine, USA), with a 14-inch screen. Printed films were not used. The eFilm 2.0 program (Merge Healthcare Inc., Chicago, USA), which provides a DICOM (Digital Imaging Communication in Medicine) reading, was used to visualize and analyze the images. The MR images were considered the standard parameter in this study.

Statistical analysis

A descriptive analysis was performed using mean, median, standard deviation, and both maximum and minimum values. The SPSS for Windows program, version 13.0 (SPSS Inc., Chicago, USA) was used for all the statistical tests. Inter-observer agreement as regards MRI staging, T stage, N stage and grouping by stages was analyzed using Cohen's kappa index. A statistical significance level of 95% (p value < 0.05) and a 5% error level were considered for the analyses. Interpretation criteria of the kappa index recommended by Landis and Koch[17] were used to analyze the results.

Results

Table 2 shows that agreement for the T stage was excellent (k = 0.85) between Observers 1 and 2 (oral radiologists) and moderate (k = 0.47) between Observers 3 and 4 (medical radiologists).

All four observers presented different results for the T stage using the clinical and MRI examinations. The highest rate of agreement (k = 0.46 = moderate) was presented by Observer 4.

Table 3 shows that agreement for the N stage was substantial (k = 0.69) between Observers 1 and 2 (oral radiologists) and considerable (k = 0.38) between Observers 3 and 4 (medical radiologists).

All four observers presented different results for the N Stage using the clinical and MRI examinations.

Table 4 shows that the agreement for grouping by

Table 2 - Inter-observer and clinical and MRI examination agreement for T Stage.

	Obs. 1	Obs. 2	Obs. 3	Obs. 4
Clinical T	k = 0.29 (p = 0.116)	k = 0.31 (p = 0.100)	k = 0.17 (p = 0.366)	k = 0.46 (p = 0.012)*
Obs. 1		K= 0.85 (p < 0.000)*	k = 0.42 (p = 0.024)*	k = 0.58 (p = 0.001)*
Obs. 2			k = 0.57 (p = 0.003)*	k = 0.73 (p < 0.000)*
Obs. 3				k = 0.47 (p = 0.006)*

k = kappa value; *p < 0.05 = statistically significant agreement; Obs. = observer; 1 and 2 = oral radiologists; 3 and 4 = medical radiologists.

Table 3 - Inter-observer and clinical and MRI examination agreement for N Stage.

	Obs. 1	Obs. 2	Obs. 3	Obs. 4
Clinical N	k = 0.35 (p = 0.115)	k = 0.69 (p = 0.003)*	k = 0.47 (p = 0.056)	k = 0.69 (p = 0.001)*
Obs. 1		k = 0.69 (p = 0.003)*	k = 0.84 (p < 0.000)*	k = 0.24 (p = 0.274)
Obs. 2			k = 0.84 (p < 0.000)*	k = 0.55 (p = 0.014)*
Obs. 3				k = 0.38 (p = 0.075)

k = kappa value; *p < 0.05 = statistically significant agreement; Obs. = observer; 1 and 2 = oral radiologists; 3 and 4 = medical radiologists.

Table 4 - Inter-observer and clinical and MRI examination agreement for Group Staging.

	Obs. 1	Obs. 2	Obs. 3	Obs. 4
Clinical Grouping	k = 0.31 (p = 0.100)	k = 0.31 (p = 0.100)	k = 0.13 (p = 0.509)	k = 0.44 (p = 0.022)*
Obs. 1		k = 0.72 (p < 0.000)*	k = 0.72 (p < 0.000)*	k = 0.44 (p = 0.017)*
Obs. 2			K = 0.58 (p = 0.001)*	K = 0.72 (p < 0.000)*
Obs. 3				K = 0.44 (p = 0.014)*

k = kappa value; *p < 0.05 = statistically significant agreement; Obs. = observer; 1 and 2 = oral radiologists; 3 and 4 = medical radiologists.

stages was substantial (k = 0.72) between Observers 1 and 2 (oral radiologists) and moderate (k = 0.44) between Observers 3 and 4 (medical radiologists).

All four observers presented different results for the grouping by stages using the clinical and MRI examinations. The highest rate of agreement (k = 0.44 = moderate) was presented by Observer 4.

Table 5 shows that there was significant agreement (p < 0.05) between the clinical and MRI staging assessments made by one oral radiologist (Observer 2) for N stage, and significant agreement between those made by one medical radiologist (Observer 4) for T and N stages and for grouping by stages.

As to MRI staging, there was significant agreement (p < 0.05) among all four observers for T stage and for grouping by stages, and there was no significant agreement between Observers 1 and 4, or between 3 and 4, for N stage. In all other comparisons, there was significant agreement (p < 0.05) for N stage (Table 6).

Discussion

The results of the present study contribute to recognizing the importance of MRI examination in establishing the staging of oral cancer.

Carcinoma lesions in the oral cavity are very aggressive and usually infiltrate the surrounding tissue and lymph vessels, producing metastasis in the cervical region.[2,18]

CT and MRI examinations are the most significant methods of diagnostic imaging in the preoperative staging of head and neck tumors, because they provide information on the extent of the lesion, infiltration of large vessels and lymph node metastasis, thereby facilitating treatment planning and prognosis.[12-14,19] During the preoperative phase of a patient's squamous cell carcinoma, CT scans are essential for evaluating the primary lesion and the possibility of bone invasion, and especially for defining involvement in cervical lymph node chains.[12-14,19] In the preoperative treatment of oral cancer, it has been shown that MRI is better for evaluating soft tissue, bone marrow involvement and perineural invasion,

Table 5 - Agreement between clinical and MRI staging assessments for all four observers.

Agreement between clinical and MRI staging	T stage	N stage	Grouping
clinical × oral radiologist (Obs. 1)	k = 0.29	k = 0.35	k = 0.31
clinical × oral radiologist (Obs. 2)	k = 0.31	k = 0.68*	k = 0.31
clinical × medical radiologist (Obs. 3)	k = 0.17	k = 0.47	k = 0.13
clinical × medical radiologist (Obs. 4)	k = 0.46*	k = 0.69*	k = 0.44*

k = kappa value; *p < 0.05 = statistically significant agreement; Obs. = observer.

Table 6 - Inter-observer agreement for MRI staging.

Inter-observer agreement	T stage	N stage	Grouping
oral radiologist 1 × oral radiologist 2	k = 0.85*	k = 0.69*	k = 0.72*
oral radiologist 1 × medical radiologist 3	k = 0.42*	k = 0.84*	k = 0.72*
oral radiologist 1 × medical radiologist 4	k = 0.58*	k = 0.24	k = 0.44*
oral radiologist 2 × medical radiologist 3	k = 0.57*	k = 0.84*	k = 0.58*
oral radiologist 2 × medical radiologist 4	k = 0.73*	k = 0.55*	k = 0.72*
medical radiologist 3 × medical radiologist 4	k = 0.47*	k = 0.38	k = 0.44*

k = kappa value; *p < 0.05 = statistically significant agreement.

and has been particularly decisive in the diagnosis of small lesions.[7,20,21]

The discrepancies found in the comparisons between the staging established by clinical and MRI examinations demonstrate the importance of this study. A clinical staging assessment lower than the real staging could result in ineffective treatment and/or increase the possibility of recurrence in a particular case, whereas a higher clinical staging assessment could lead to more radical treatment, thereby increasing treatment aftereffects. The related literature states that appropriate staging of a lesion is essential for decision-making during surgical and/or radiotherapy planning, for predicting the prognosis and for deciding how to carry out patient follow-up to guarantee greater life expectancy and cure.[1,2,7]

Different results were found between the clinical and MRI examinations for T staging. If a clinical staging assessment establishes a primary tumor as smaller than it really is, this could result in ineffective surgical margins and in an incomplete removal of the lesion.[7] Figures 1 through 3 show case number 8 clinically staged as T1, in which the MRI shows the primary tumor measuring 3.4 cm (T2). Surgical and anatomic pathology confirmation would be necessary to determine the actual size of the primary tumor.

Agreement among all four observers was significant for MRI T staging. This agreement shows that MR images provide greater interpretation standardization. Calibration of the observers may have been decisive in achieving the agreement levels and should be used in joint training programs that prepare medical and oral radiologists to diagnose oral cancer at reference centers providing multidisciplinary care.[15]

There was substantial and significant agreement between the clinical and MRI staging performed by Observers 2 and 4 for N stage. Nevertheless, case number 3, clinically staged as N1, was staged as N0 by two observers (1 and 3) in the MRI examination. A higher clinical staging assessment, establishing a false-positive for regional metastasis, may lead to more radical treatment and increase morbidity. According to Malard *et al.*[10] and Scully and Bagan,[11] a combination of both clinical and imaging examinations is essential for the detection of metastatic cervical lymph nodes, and could improve staging and prognosis determination.

Agreement between Observers 1 and 2, 1 and 3, 2 and 3, and 2 and 4 in the MRI staging was significant, indicating that the pre-established criteria and image interpretation guide could also have been crucial for the level of agreement achieved for the N stage.

Different results were observed for the clinical

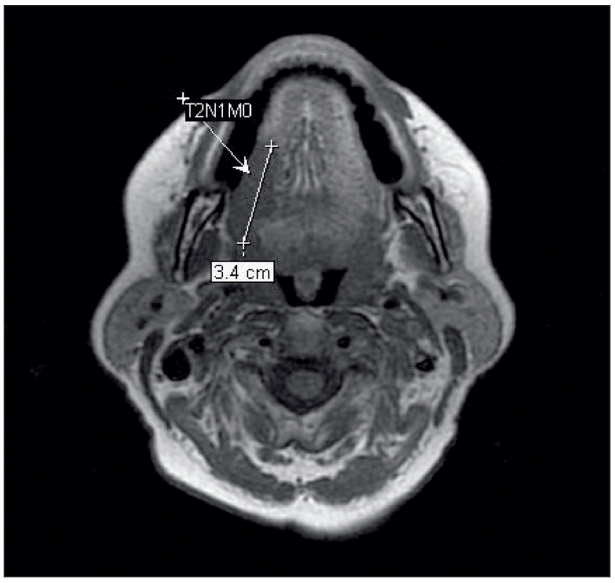

Figure 1 - MRI axial slice, T_1-weighted, without contrast, showing a tumor of isosignal intensity at the base of the tongue (arrowhead), on the right side, measuring approximately 3.4 cm.

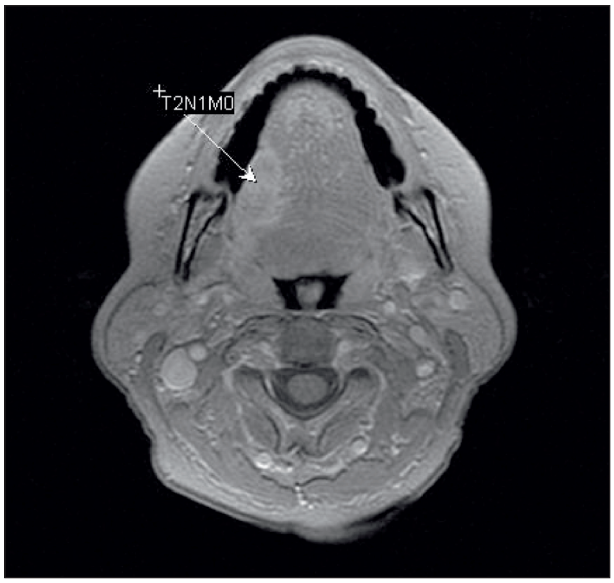

Figure 2 - MRI axial slice, T_1-weighted, with contrast, showing a tumor of hyper-signal intensity (enhanced with contrast) at the base of the tongue (arrowhead), on the right side.

Figure 3 - MRI coronal slice, T_2-weighted, showing a tumor of isosignal intensity at the base of the tongue (arrowhead), on the right side.

and MRI staging, and agreement was significant only for Observer 4. Among these results, three cases were staged as belonging to the IVA grouping, which represents lesions which are larger and at a more advanced stage, thereby facilitating diagnosis.[15] This confirms the greater importance of the MRI examination for smaller lesions. The definition of grouping by stages is critical in determining the patient's treatment plan, prognosis and survival span.

Agreement among all four observers for stage grouping using MRI was significant, and greater between the oral radiologists. Based on these results and on literature data, it could be stated that clinical examination, anatomic pathology testing and diagnostic imaging modalities (which could include CT and MRI) are necessary to establish the staging of patients with oral cancer. According to Weber *et al.*[13] and Scully and Bagan,[22] CT and MRI examinations seem to be the most important diagnostic tools when establishing pre-therapeutic staging of head and neck tumors. CT is essential, insofar as it provides a better evaluation of cervical lymph node involvement and invasion of bone cortices adjacent to the primary tumor area. The MRI examination provides a better evaluation of the soft tissues affected by the lesion and allows a more thorough evaluation of small tumors. This examination should be part of the treatment protocol of patients with oral cancer, depending on its availability, accessibility and the possibility of carrying out the examination. According to Warnakulasuriya,[4] improvement in the quality of healthcare helps to reduce mortality rates.

While the results would indicate the importance of using MRI in the diagnosis of oral cancer, there is also a very obvious need for a combination of research and surgical and pathological information to identify sources of error in pretreatment staging. Joint training initiatives and calibration of medical and oral radiologists should be promoted to provide an improved multidisciplinary approach to oral cancer.

Conclusion

There was no agreement between the staging established by clinical and MRI examinations for oral cancer. MRI examination is useful to provide a better assessment of TNM staging, and the examinations should be analyzed by different professionals (physicians and dentists) in a multidisciplinary approach.

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