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ORIGINAL ARTICLE

Relationship between the appearance of tongue carcinoma on intraoral ultrasonography and neck metastasis

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Abstract
Objective To evaluate the usefulness of intraoral ultrasonography (IOUS) as a tool for predicting neck metastasis.
Introduction Squamous cell carcinoma (SCC) of the tongue is aggressive and has a great propensity to metastasize to cervical lymph nodes. SCC of the oral cavity has a worse prognosis when associated with metastatic cervical nodes. Therefore, the metastatic potential of tongue carcinoma should be graded preoperatively to help determine the requirement for neck dissection.
Methods Nineteen patients (11 men, 8 women) between 36 and 79 years of age (mean age 60) with T1 to T4a TNM-stage tongue carcinomas were evaluated preoperatively with IOUS. Clinical and pathological TNM classifications were performed.
Results The average tumor thicknesses measured using histological sections were significantly ($p < 0.01$) lower than those with IOUS (1.3 vs. 1.6 cm, respectively). A significant correlation was observed between the tumor thickness measured using ultrasonography and that measured using histological sections (pathology). Based on this greater accuracy, the cutoff point of tumor thickness based on IOUS evaluation for predicting neck metastasis was determined to be 1.8 cm.
Discussion Some factors may influence neck metastasis. A knowledge of these would help to avoid unnecessary surgical intervention for N0 patients. The results of this study indicates that there is a significant correlation between neck metastasis and tumor thickness.
Conclusion Intraoral ultrasonography is useful tool for identifying tongue tumors and measuring their thickness, with the thickness measured by IOUS showing a very good correlation with histological measurements. Moreover, IOUS provides prognostic information prior to surgical treatment since tumor thickness can predict the chance of recognizing metastatic cervical nodes.

Keywords Intraoral ultrasonography · Tongue carcinomas · Histopathological correlation · Squamous cell carcinoma · Malignant tongue tumors

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Introduction

The prevalence of oral cancer in Brazil is high, reaching 14,000 cases in 2005 [1]. Mouth cancer ranks eighth among malignant tumors in the Brazilian population and sixth when only men are considered. The most common site in the mouth is the tongue, with a reported incidence of 17.8–52% [2]. In the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, about one-third of all oral cancers are located on the tongue [3]. Squamous cell carcinoma (SCC) is the most common histological type

of malignant tumor found in the oral mucosa, accounting for over 90% of all cases [3].

SCC of the tongue usually is very aggressive and has a great propensity to metastasize to cervical lymph nodes. However, SCC of the oral cavity has an even worse prognosis when associated with metastatic cervical nodes [4]. Therefore, the metastatic potential of tongue carcinoma should be graded preoperatively to help determine the requirement for neck dissection [5].

The value of clinical, pathological, and imaging parameters and of molecular markers as predictors of neck metastasis in oral cancer has been investigated [6–9]. One of the most important factors associated with the development of nodal metastases is the thickness (i.e., the depth of invasion) of the lesion, with the thickness of squamous carcinoma being directly related to the presence of nodal metastasis. In this landscape, an accurate, noninvasive method capable of detecting and measuring tumor thickness has the potential to be relevant, since therapeutic procedures could be improved. To obtain such information preoperatively, digital palpation, computed tomography (CT), magnetic resonance imaging (MRI), and biopsies for histopathological examination are performed routinely.

Digital examination depends on the ability and experience of the examiner and obviously has a low accuracy and objectivity. CT and MRI have a number of limitations related to the evaluation of the precise size and extent of the tumor, small lesions or the presence of metal artifacts can be confounding factors [10]. A histopathological examination following a biopsy is useful, not only for confirming the diagnosis but also for estimating the malignant potential of the lesion; however, grading tumor invasion accurately from a biopsy is difficult because only a limited part of the tumor tissue is sampled [5]. Ultrasonography is a noninvasive, rapid, easily repeatable, and inexpensive examination. Intraoral scanning of the tongue lacks the disadvantages of CT and MRI and provide give precise information on invasive tumors for predicting neck metastasis, especially in the clinically normal neck [5, 10].

In the study reported here, we examined the usefulness of intraoral ultrasonography (IOUS) as a tool for predicting neck metastasis and delineating the extent of the tumor based on a comparison with the histopathological findings.

Materials and methods

Nineteen patients (11 men, 8 women) between 36 and 79 years of age (mean age 60 years) with T1 to T4a TNM-stage tongue carcinomas were evaluated preoperatively by IOUS between February 2006 and January 2009 (Table 1). The examinations were performed at the Institute of Radiology of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo.

Based on the surgeon's inspection and digital palpation (RAM), the clinical growth pattern was classified as superficial, exophytic, or endophytic. Endophytic, exophytic, and superficial lesions were observed in two (10.5%), two (10.5%), and 15 (78.9%) patients, respectively. Clinical and pathological TNM classifications were also determined. Of the 19 patients, two (11.8%), eight (47.1%), one (5.9%), and six (35.3%) had T1 to T4 lesions, respectively; the grading of the two remaining patients was not precise.

For the N0 neck (14 patients initially), an expectant follow-up approach was used, except for one patient who had enlarged lymph nodes seen only on the initial cervical US examination. Follow-up to detect lymph node metastasis in the remaining 13 patients consisted of a physical examination and cervical US or neck-enhanced CT. These participants were followed every month for the first year and every 3–4 months for at least 2 years after the initial treatment. The minimum and mean follow-up periods were 24 and 26.8 months, respectively. Delayed neck metastasis was detected by cervical US in two patients after the primary operation. These two individuals underwent neck dissection, as did the patients who were initially diagnosed with metastatic neck lymph nodes.

After the initial examinations and critical follow-up, one (5.3%) patient was classified as N1, four (21.1%) patients as N2, one (5.3%) patient as N3, and 13 (68.4%) patients as N0. None of these patients showed evidence of distant metastasis at any time after the initial examination.

Sonographic technique

B-mode intraoral scanning was performed using a gray-scale US system (Logiq 500; GE Medical Systems, Milwaukee, WI) attached to a T-shaped intraoperative transducer (H40212LM/T739 T-Type; GE Medical Systems) thinly coated with sterile gel and covered with a rubber sheath (Fig. 1). This probe is characterized by a 5- to 10-MHz pulsed ultrasonic beam (field-of-view 39 mm) and a 44 × 10-mm linear array. To image the tumor, the probe was placed on the tumor surface so as not to compress the tissues. A water-filled cuff was used in some cases to facilitate positioning of the probe. All IOUS examinations were performed by the same operator (MCC) to maintain objectivity.

The pattern of the tumor margin was classified as well circumscribed (type 1), moderately clear (type 2), or diffuse, unclear (type 3).

Sonographic examinations were performed within 48 h preoperatively when the patient was hospitalized.

Table 1 Data and staging of the cases studied

Case	Age (years)	Gender	US thickness (cm)	Histological thickness (cm)	Ultrasound margins[a]	Type	Grade	Depth of lesion	Inflammatory[b]	Lymph node
1	38	F	0.78	0.6	2	Exophytic	I	Muscle	3	–
2	75	F	1.2	1.1	2	–	II	–	2	+
3	44	F	1.2	1.2	2	–	I	Muscle	2	+
4	47	M	2.4	2	3	Endophytic	II	Muscle	2	+
5	74	M	1.2	1	3	Exophytic	I	Muscle	2	–
6	57	M	1.1	0.7	3	–	I	Muscle	1	–
7	36	M	2.1	2.4	3	–	II	Muscle	2	+
8	49	M	1.8	1.8	1	–	I	Muscle	–	+
9	68	M	3	2	1	–	I	Muscle	–	+
10	49	M	2.8	1.5	3	–	I	Other structures	2	+
11	48	M	0.9	0.6	3	–	I	Muscle	2	–
12	74	F	1.1	1.1	1	–	–	–	–	–
13	64	M	1.58	1	3	–	I	Muscle	–	–
14	79	F	0.54	0.5	2	–	I	Muscle	–	–
15	75	M	3.5	3.5	2	–	II	Other structures	1	+
16	66	F	1.28	1.2	3	–	I	Muscle	2	–
17	70	F	0.75	1	1	–	I	–	3	–
18	56	M	2	0.7	2	Endophytic	II	Other structures	1	–
19	71	F	0.7	0.9	–	–	III	Muscle	–	–

US ultrasonagraphy, *F* female, *m* male

[a] 1, Well-circumscribed margin; 2, moderately clear margin; 3, diffuse and unclear margins

[b] 1, Minimal lymphoplasmacytic infiltration with very few or small groups of lymphocytes at the periphery; 2, moderate lymphoplasmacytic infiltration with multiple, but scattered foci, at the edge and beneath the tumor nest; 3, marked lymphoplasmacytic infiltration occasionally forming band-like confluence

Fig. 1 High-frequency T-type linear array probe with lateral field-of-view, coated with sterile gel and covered with a rubber sheath

Histological data

The surgical specimens removed from the 19 patients were examined microscopically with hematoxylin–eosin (H&E) staining. The slides were reviewed, and the following variables were considered:

1. Histological grade: well differentiated (grade I), moderately differentiated (grade II), or poorly differentiated (grade III) carcinoma;
2. Inflammatory cell infiltration was classified into three groups: (1) minimal lymphoplasmacytic infiltration, with very few or small groups of lymphocytes at the periphery (type 1); (2) moderate lymphoplasmacytic infiltration with multiple, but scattered foci at the edge and beneath the tumor nest (type 2); (3) marked lymphoplasmacytic infiltration occasionally forming a band-like confluence (type 3);
3. Histological tumor thickness was measured in each section using an ocular micrometer. The thickness was measured vertically, starting from the surface of both exophytic and endophytic tumors, up to the maximum point of invasion [11–13];
4. The presence metastatic of lymph nodes.

The histological analysis was performed at the Pathologic Anatomy Service of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo. All

cases were reviewed by the senior pathologist (RG) involved in this study.

Statistics

The correlations between neck metastasis and the variables studied were analyzed using the chi-square test and Student's *t* test for parametric data. Linear regression analysis was performed, and scatterplots of the imaging measurements versus the pathology measurements were generated. The cutoff point of tumor thickness associated with neck metastasis was determined as the lowest cutoff value with the maximum accuracy according to the true-positive and true-negative rates. All these analyses were performed using the SPSS statistical package (SPSS, Chicago, IL). The level of significance was $p < 0.05$.

Ethics

This study and the informed consent form were approved by our institution's Committee of Ethics in Research. All patients signed the informed consent form with no restrictions.

Results

Intraoral sonography identified all of the tongue lesions. Close examination of the findings revealed that the sonographic pattern of the normal tongue was homogeneous echogenic tissue, while the tumors were hypoechoic (Fig. 2). When an ulcerated area was present, a hyperechoic image was visualized with posterior sonography attenuation due to air interpositioning (Fig. 3).

The average thickness measured with IOUS was 1.6 cm (range 0.5–3.5 cm). Of the 19 cases, 16 (84.2%) lesions were located at lateral margins of the tongue, and one (5.3%) each was on the ventral part of the tongue, at the vertex of the tongue, and compromised the entire tongue.

The average thickness measured in the histological sections was 1.3 cm (range 0.50–3.5 cm), which is significantly ($p < 0.01$) lower than the IOUS measurements. A significant correlation was observed between the tumor thicknesses measured using US (σ) and the pathological findings (ρ). The correlation formula determined in the linear regression analysis was $\rho = (0.7373)\sigma + 0.1438$. A significant Pearson correlation ($p < 0.001$) was detected, and the correlation coefficient was $R = 0.83$ (Fig. 4).

Using the maximum accuracy, the cutoff points for the US and histological tumor thickness for predicting neck metastasis were determined to be 1.8 and 1.1 cm, respectively (Tables 2, 3).

Among the histopathological parameters, only tumor thickness was a significant predictor of metastasis in both univariate and multivariate log-linear univariate analyses (Table 4). Muscle invasion, histological grade,

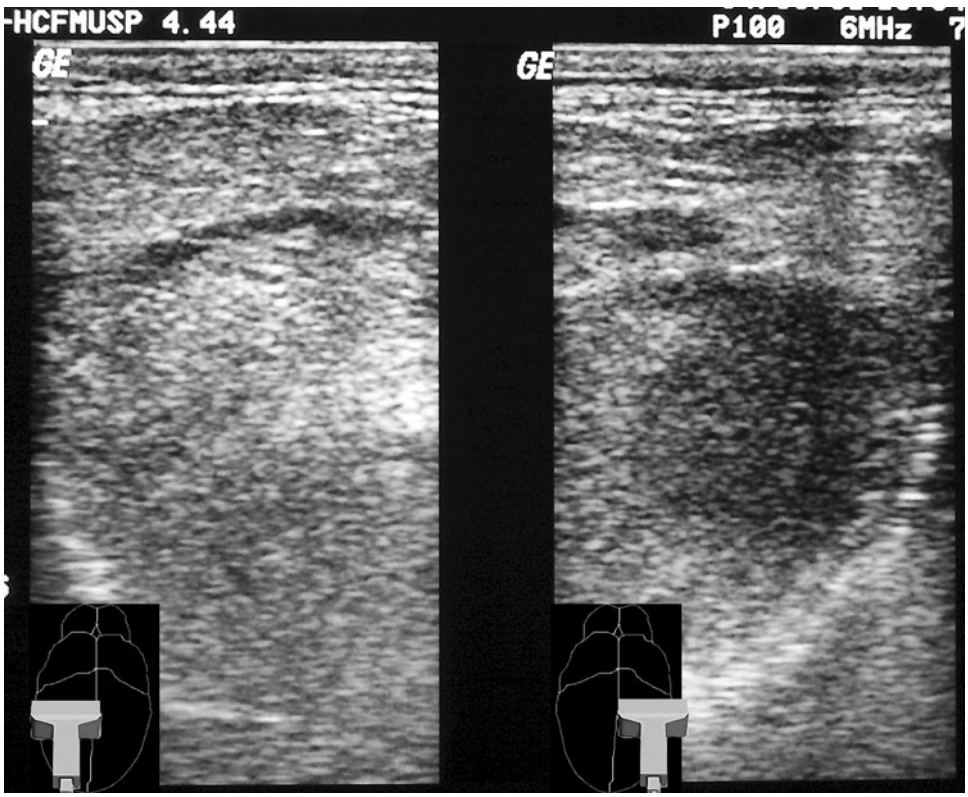

Fig. 2 *Left* Sonographic pattern of the normal tongue (homogeneous echogenic tissue), *right* the tumor nodule with irregular edges and hypoechoic tissue

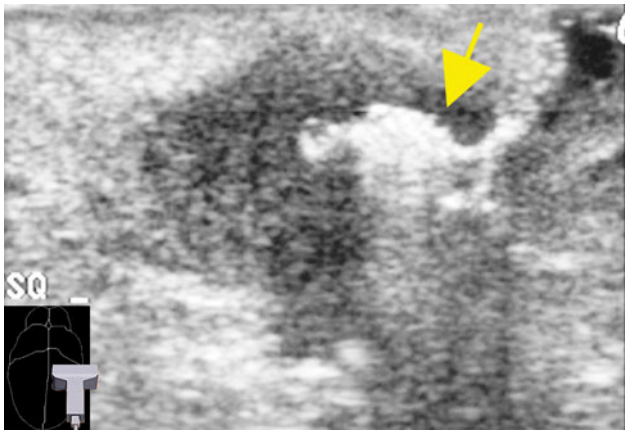

Fig. 3 Sonographic appearance of a tongue with ulcerated squamous cell carcinoma. Note the presence of hyperechoic air (*arrow*) and its sonographic attenuation

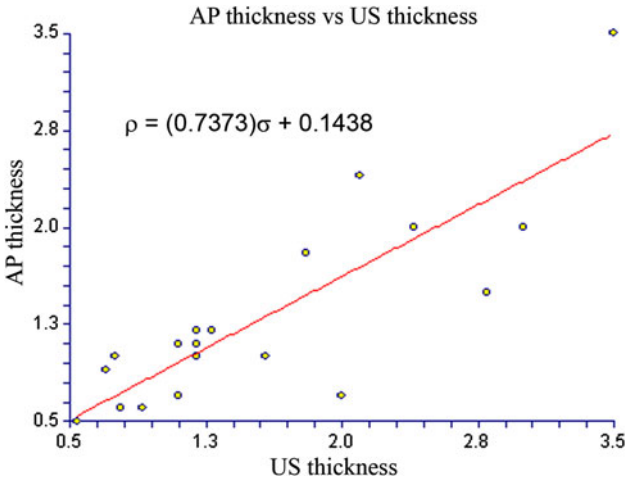

Fig. 4 Linear correlation between ultrasonography and histological thickness. *AP* Anterior-to-posterior

inflammatory cell infiltration, and desmoplasia were not correlated with neck metastasis ($p > 0.05$).

Of the 19 (42.1%) patients, eight had metastatic lymph nodes. A tumor with a thickness >1.8 cm measured by IOUS and 1.1 cm measured in the histological sections had a higher probability of metastatic cervical lymph nodes.

Regarding the margins seen on US, two (25%) were type 1, three (37.5%) were type 2, and three (37.5%) were type 3 when positive lymph nodes were found. For negative lymph nodes, two (20%) were type 1, three (30%) were type 2, and five (50%) were type 3 (Table 1).

Table 2 Thickness of the tumor measured by intraoral ultrasonography as a function of sensitivity, specificity, and accuracy at predicting metastasis

Cutoff value (cm)	Ultrasound thickness		
	Sensitivity	Specificity	Accuracy
0.54	1.00	0.00	0.42
0.7	1.00	0.09	0.47
0.75	1.00	0.18	0.53
0.78	1.00	0.27	0.58
0.9	1.00	0.36	0.63
1.1	1.00	0.45	0.68
1.2	1.00	0.64	0.79
1.28	0.75	0.73	0.74
1.58	0.75	0.82	0.79
1.8[a]	0.75	0.91	0.84
2	0.63	0.91	0.79
2.1	0.63	1.00	0.84
2.4	0.50	1.00	0.79
2.8	0.38	1.00	0.74
3	0.25	1.00	0.68
3.5	0.13	1.00	0.63

[a] Cutoff for tumor thickness determined by intraoral ultrasonography (IOUS) for predicting neck metastasis

Table 3 Histological thickness of the tumor as a function of sensitivity, specificity, and accuracy at predicting metastasis

Cutoff value (cm)	Histological thickness		
	Sensitivity	Specificity	Accuracy
0.5	1.00	0.00	0.42
0.6	1.00	0.09	0.47
0.7	1.00	0.27	0.58
0.9	1.00	0.45	0.68
1	1.00	0.55	0.74
1.1[a]	1.00	0.82	0.89
1.2	0.88	0.91	0.89
1.5	0.75	1.00	0.89
1.8	0.63	1.00	0.84
2	0.50	1.00	0.79
2.4	0.25	1.00	0.68
3.5	0.13	1.00	0.63

[a] Cutoff for tumor thickness determined by the histological procedure for predicting neck metastasis

Discussion

Cervical lymph nodes metastasis indicates a poorer prognosis in patients with tongue cancer [14]. Neck dissection is the standard treatment for metastatic neck lymph nodes. The reported incidence of neck metastasis of tongue SCC is relatively high, namely, 37–53% [13, 15–17]; in our study, it was 42.1%.

Table 4 Pathological parameters, neck metastasis, and their univariate and multivariate analyses

Pathologic parameters	Neck metastasis						Univariate analysis	Multivariate analysis
	Positive lymph nodes ($n = 8$)		Negative lymph nodes ($n = 11$)		Total ($n = 19$)			
	n	%	*n*	%	*n*	%	*p* value	*p* value
AP tumor thickness							<0.001	NS
≥1.1 cm	8	100.0	2	18.2	10	52.6		
<1.1 cm	0	0.0	9	81.8	9	47.4		
Muscle invasion							0.3747	NS
Present	5	62.5	8	72.7	13	68.4		
Absent	3	37.5	3	27.3	6	31.6		
Inflammatory cell infiltration							0.2499	NS
Type 1	1	16.7	2	28.6	3	23.1		
Type 2	5	83.3	3	42.8	8	61.5		
Type 3	0	0.0	2	28.6	2	15.4		
Histological grade							0.1381	NS
Grade I	4	50.0	8	80.0	12	66.7		
Grade II	4	50.0	1	10.0	5	27.8		
Grade III	0	0.0	1	10.0	1	5.6		

NS not significant: $p > 0.05$

To avoid unnecessary surgical intervention for N0 patients, some studies have examined factors that may influence neck metastasis [5, 18, 19]. We found a significant correlation between neck metastasis and tumor thickness, in that tumor thickness was the most important histological predictor of neck metastasis. However, some reports have suggested that the depth of muscle invasion is strongly associated with the risk of occult metastasis [5, 20–22]. Accordingly, the critical aspect in the growth of a tongue tumor is likely to be the deep invasion into the tongue musculature. The mode of invasion, muscle invasion, stromal reaction, and histological grade were not significant predictors of neck metastasis in our series, possibly due to our small sample size.

Many studies have reported that tumor thickness is an important predictor of cervical lymph node metastasis [5, 7, 23–29]. We determined that a tumor thickness of 1.1 cm according to histological tests or 1.8 cm according to the IOUS scans were the cutoff points for predicting the risk of neck metastasis of tongue cancer. This finding suggests that lymph node scanning should be performed more carefully when the tumor thickness exceeds 1.8 cm. In addition, minimal lymph node changes and muscle invasion should be overlooked to improve sensitivity and give the surgeon a better surgical plan.

IOUS is a sensitive method that is capable of measuring tongue-tumor thickness. We found a slight discrepancy between the IOUS-based and histological section-based measurements. However, the overestimation based on the IOUS scans was not large enough to bias the correlation between the two variables. In addition, they were not related to the degree of inflammatory infiltration or tumor desmoplasia. This discrepancy may have been due to the reduction or contraction of the specimen after formalin tissue fixation and slide preparation [30]. As a result, it can be concluded that US images reflect the actual tumor thickness more precisely than the measurements obtained using histological sections [5].

The main technical limitation of IOUS was apparent when large or posterior lesions were present, primarily due to both the difficulty in accessing the posterior tongue with the probe and from the induction of vomiting. In some cases, problems occurred due to tongue movements, which were overcome by asking the patient to hold his/her own tongue.

The very good correlation between lesion size and metastatic lymph nodes can help in planning the treatment regimen and indicate the disease prognosis.

The results of this study suggest that IOUS is capable of identifying tongue tumors and measuring their thickness with a very good correlation to the thickness determined using histological sections. Moreover, IOUS gives preoperative prognostic information, since tumor thickness predicts the chance of recognizing metastatic cervical nodes. Consequently, IOUS assessment of tumor thickness provides useful information, enabling the most advantageous treatment for patients with tongue cancer in mainly early-stage tumors.

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Conflict of interest None declared.

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