



Comparative assessment of the depth of invasion of early-stage oral cavity carcinomas based on intraoral ultrasound and computerized tomography findings

Komparativna procena dubine invazije tumora usne duplje u ranom stadijumu na osnovu nalaza intraoralnog ultrazvuka i kompjuterizovane tomografije

Biljana Marković Vasiljković*†, Svetlana Antić*†, Drago Jelovac*‡

University of Belgrade, *Faculty of Dental Medicine, †Center for Radiological Diagnostics, Belgrade, Serbia; ‡Clinic for Maxillofacial Surgery, Belgrade, Serbia

Abstract

Background/Aim. The depth of invasion of oral cavity carcinoma (OCC) and the nodal involvement define the treatment selection, outcome, and prognosis of the disease. In determining the stage of OCC, the most widely applied methods are computerized tomography (CT) and magnetic resonance imaging (MRI), whose limitations can be overcome to some extent by using intraoral ultrasound (IOUS). The aim of the study was to evaluate the imaging presentation of early-stage OCC, determine the depth of invasion (DOI) and the greatest diameter (GD) of the tumor using the IOUS and CT methods, and compare them with histopathological (HP) findings. **Methods.** The study was designed as a prospective one, with a time limitation of three months. Eleven patients with clinical early-stage OCC underwent a native CT examination of the head and neck as well as a contrast-enhanced phase, and then IOUS of the lesion was performed. Using both methods, DOI and GD values were measured, and the values were correlated with HP findings. The analysis of the obtained data was performed using the statistical package SPSS 22 and Pearson correlation coefficient. **Results.** A significant correlation ($p = 0.001$) was established between the DOI values measured by IOUS and CT examination with the measurements obtained by HP processing. On the other hand, by comparing the GD measured on IOUS and CT examination, no correlation was established with the HP report. **Conclusion.** Measurements of DOI obtained by IOUS significantly correlated with those in the HP report, while overcoming the limitations of the CT method in the evaluation of small-sized tumors and tumors that cannot be shown due to artifacts.

Key words:

histological techniques; mouth neoplasms; neoplasm invasiveness; tomography, x-ray computed; ultrasonography.

Apstrakt

Uvod/Cilj. Dubina invazije karcinoma usne duplje i zahvaćenost regionalnih limfnih čvorova definišu terapijski modalitet, ishod lečenja i prognozu bolesti. U određivanju stadijuma karcinoma usne duplje, najšire primenjivane metode su kompjuterizovana tomografija (KT) i magnetna rezonanca (MR), čija ograničenja se donekle mogu prevazići upotrebom intraoralnog ultrazvuka (IOUZ). Cilj rada bio je da se proceni vizuelni prikaz karcinoma usne duplje ranog stadijuma, odredi dubina invazije (DI) i najveći dijametar tumora (NDT) metodama IOUZ i KT, a zatim da se uporede sa histopatološkim (HP) nalazom. **Metode.** Studija je dizajnirana kao prospektivna sa vremenskim ograničenjem od tri meseca. Kod 11 bolesnika sa ranim kliničkim stadijumom karcinoma usne duplje, urađen je nativni i postkontrastni pregled glave i vrata pomoću KT, a potom pregled lezije metodom IOUZ. Koristeći obe metode mere su vrednosti DI i NDT, koje su potom korelisane sa HP nalazom. Analiza dobijenih podataka izvršena je upotrebom statističkog paketa SPSS 22 i Pearson-ovog koeficijenta korelacije. **Rezultati.** Ustanovljena je značajna korelacija ($p = 0,001$) između vrednosti DI izmerenih pomoću metoda IOUZ i KT, sa merama dobijenim HP obradom. Sa druge strane, upoređivanjem vrednosti za NDT izmerenih na IOUZ i KT pregledu, nije ustanovljena korelacija sa HP izveštajem. **Zaključak.** Mere DI dobijene metodom IOUZ značajno su korelisale sa onim u HP izveštaju, uz prevazilaženje ograničenja KT metode u evaluaciji tumora malih dimenzija i tumora koji se zbog artefakata ne mogu prikazati.

Ključne reči:

histološke tehnike; usta, neoplazme; neoplazme, invazivnost; tomografija, kompjuterizovana, rendgenska; ultrasonografija.

Introduction

Malignancies of the oral cavity are the most common malignancies of the head and neck¹. Tongue is the origin of tumors in half of the cases from developed countries². Smoking, alcohol, and, to a lesser extent, human papillomavirus (HPV) infection are the risk factors for oral cavity carcinoma (OCC)². The incidence of different localizations of OCC, in addition to the socio-epidemiological status, also depends on the habits of the population^{1,2}. In Eastern European countries, the frequency of carcinoma of the tongue is higher, while due to the habit of chewing tobacco, squamous cell carcinoma (SCC) in the lower gingivobuccal sulcus is the most common sublocation of OCC in India³.

The 2010 staging manual of OCC incorporates the greatest diameter (GD) of the tumor as a relevant factor for determining the stage of the primary tumor and as a prognostic factor for disease-specific survival (DSS), but also for progression-free survival (PFS)⁴. The updated 8th edition of the American Joint Committee of Cancer (AJCC) 2017 introduces depth of invasion (DOI) as the independent prognostic factor of OCC⁵. Recently, a retrospective study indicated that DOI is a prognostic factor only for the DSS in patients with early stage OCC, along with cofactors such as lympho-vascular invasion and histopathological (HP) tumor grade⁶.

The most common imaging methods for tumor staging and evaluating DOI are computerized tomography (CT), magnetic resonance imaging (MRI), and, lately, intraoral ultrasound (IOUS)³. Known limitations of CT and MRI for OCC examination are artifacts originating from metal dental restorations. On the other hand, a limiting factor of IOUS is the eventual inaccessibility of the lesion and the impossibility of its complete coverage by the probe³. These methods should be complementary to achieve the best diagnostic results. To our knowledge, IOUS examinations of the OCC have not been performed in Serbia so far.

Therefore, this study aimed to evaluate the imaging presentation of early-stage OCC, to determine the DOI and GD by IOUS and CT methods, and to compare it with HP findings.

Methods

The study was designed as a prospective one and conducted with the approval of the Ethics Committee of the Faculty of Dental Medicine, University of Belgrade, Serbia (No. 36/33 from December 14, 2022).

The inclusion criteria for this research were the following: clinical T1 or T2 tumor stage, clinical and radiological N0 stage, clinical and radiological M0 stage, and accessibility of the lesion by hockey stick IOUS probe.

The exclusion criteria for this study were the following: incomplete postoperative HP report (DOI not specified), hypersensitivity to iodinated contrast media (contrast CT was missing), and surgery that was not performed.

Out of 52 patients referred to the Center for Radiological Diagnostics with an oral cavity lesion, 11 met all the inclusion criteria for the study.

Patients underwent a non-contrast and contrast-enhanced CT examination of the head and neck (ranging from the base of the skull to the upper aperture of the thorax) performed on a 64-slice machine (Philips Ingenuity Core 64, The Netherlands) in order to assess the local tumor extent and detect lympho-nodal disease. Contrast CT examination was performed in the arterial-venous phase using the split bolus technique: 60 mL + 10 s pause + 40 mL with a flow rate of 2 mL/s. Before the contrast injection, during the break, and at the end of the contrast scan, patients received saline in the following amount: 14 mL + 30 mL + 40 mL. Sections were made at 0.8 mm thickness and reconstructed at 0.625 mm in the bone and soft tissue window (IntelliSpace Portal 10, Philips, The Netherlands).

In order to better display and separate the tissues and organs in the vestibulum of the oral cavity, CT scanning was performed using the inflated cheeks technique. We instructed our patients to perform the maneuver of throwing the head back and raising the tip of the tongue to the palate for a more optimal view of the OCC of the ventral side of the tongue. Metal artifact reduction CT algorithm (OMAR, Philips, The Netherlands) was applied as well.

The IOUS was performed with the unit SonoScapeS50 PRO (Guangdong, China), using the hockey stick multifrequency probe (1012, F-5.5MHz–10MHz). A glove with a probe immersed in the gel was placed directly on the surface of the lesion. The normally present saliva served as an interface between the surface of the lesion and the surface of the glove. Ultrasound sections were made in all directions of the lesion, and the characteristic sections were forwarded to the Picture Archiving and Communication System (PACS) station.

Patient examinations (CT and IOUS) were evaluated at the PACS station independently by two radiologists. All measurements were repeated three times, and the obtained separate values of DOI and GD were expressed as the mean value.

Statistical analyses were performed using SPSS 22.0 (SPSS Statistics for Windows, SPSS, Inc., Chicago, IL, USA). Pearson's coefficient was used to show the correlation between DOI and GD values measured by IOUS and CT and corresponding HP measures⁷. The values of $p < 0.05$ were set as significant. Intraclass Correlation Coefficient (ICC) test was used to determine inter-observer reliability for measurements taken on ultrasound and CT scans. We performed a *post hoc* analysis based on the results of the study, and the achieved power was 75.8%. Power for 11 respondents was calculated for the difference between two dependent means, $\alpha = 0.05$, and the effect size was calculated based on the difference between the two dependent means and standard deviation of difference ($d_z = 0.76$, $r_h = 0.947$). That was performed in the G*power program (version 3.1.9.2.)⁸.

Results

After the surgery, all patients were diagnosed with SCC, and the HP T stage was reported as well. Seven (63.64%) patients were male, and 4 (36.36%) were female. The average age of the patients was 57.64 years (from 45 to 67 years). Nine (81.8%) patients had tongue carcinoma, and 2 (18.2%) had buccal mucosa carcinoma.

The most common site of OCC origin was the margin of the tongue (Table 1).

In 2 out of 11 patients, the lesion could not be detected by CT, but only by IOUS, due to the presence of numerous artifacts originating from metal dental restorations (Figures 1, 2, and 3 illustrate the DOI measurements assessed by IOUS and CT).

ICC interobserver tests showed a high correlation between the measured values of DOI and GD (in the range from

Table 1

Sublocations of early stage oral cavity carcinoma.

Localization	n (%)
Tongue	
lateral margin	5 (45.5)
ventral side	3 (27.3)
dorsal side	1 (9.1)
Buccal mucosa	2 (18.2)
Total	11 (100.0)

n – number. All values are expressed as numbers (percentages).

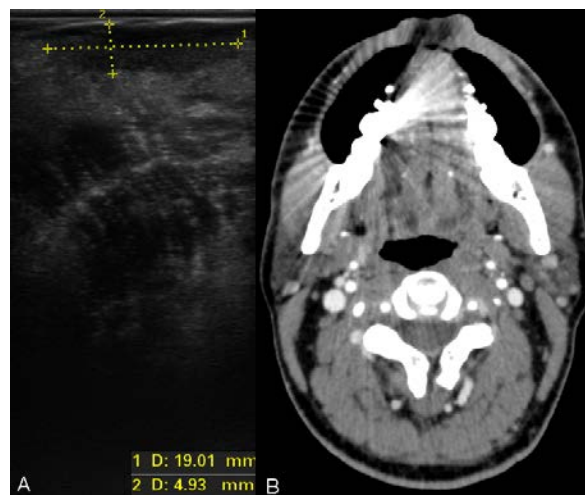


Fig. 1 – Oral cavity carcinoma (OCC) localized on the lateral edge of the tongue with measured DOI and GD: A) IOUS shows a hypoechoic and not sharply demarcated lesion towards the deeper tissues of the tongue; B) A transversal CT scan showing that it was not possible to detect OCC due to the presence of artifacts originating from metal dental restorations. IOUS – intraoral ultrasound; DOI – depth of invasion; CT – computed tomography; GD – greatest dimension.

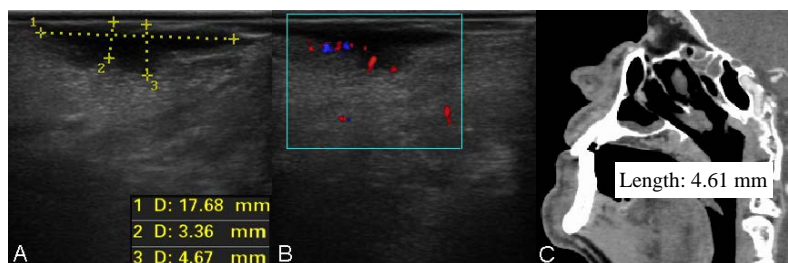


Fig. 2 – Oral cavity carcinoma (OCC) localized on the ventral side of the tongue with measured DOI and GD: A) A hypoechoic, plaque lesion with an unsharp border towards the deeper tissues of the tongue, shown by the IOUS; B) Visualization of OCC vascularization using IOUS – note the dominantly fringe distribution of Color Doppler signal (blue and red color); C) Contrast-enhanced CT in sagittal reformation with the tip of the tongue on the hard palate showing OCC with measured DOI, localized on the ventral side of the tongue. There is a well-opacified plaque lesion on the ventral side of the tongue. For abbreviations, see Figure 1.

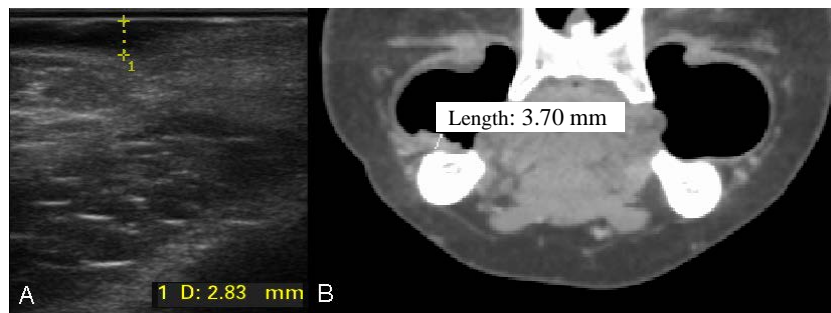


Fig. 3 – A) IOUS of oral cavity carcinoma (OCC) localized on the buccal mucosa with measured DOI. Note the hypochoic, plaque lesion with an unsharp border towards the deeper buccal tissues. B) Contrast-enhanced CT in coronal reformation and in distension technique (inflated cheeks) presenting the DOI measuring of well-opacified OCC, localized on the buccal mucosa. For abbreviations, see Figure 1.

0.959 to 1). Statistical analysis of data established a strong correlation between DOI values measured by IOUS and CT with the measurements obtained by HP processing. On the other hand, by comparing GD values assessed by IOUS and CT with HP reports, no correlation was established (Table 2).

Table 2

Correlation of DOI and GD values measured by IOUS and CT methods with the HP findings

Parameter	PCC	<i>p</i> -value
DOI		
IOUS-HP	0.947	0.001
CT-HP	0.868	0.05
GD		
IOUS-HP	0.277	0.595
CT-HP	-0.612	0.388

DOI – depth of tumor invasion; GD – greatest diameter of tumor; CT – computed tomography; PCC – Pearson's correlation coefficient; HP – histopathology; IOUS – intraoral ultrasonography.

Discussion

During the last decade, IOUS has been used in the evaluation of various benign and malignant oral cavity lesions⁹. Malignant tumors of the tongue, walls, and floor of the oral cavity are, in 90% of cases, SCCs and appear as hypochoic lesions on IOUS examination^{9,10}. Most publications refer to SCC of the tongue, which also constituted most of our study (91.8%). A systematic review from 2019 analyzed 19 published studies of different designs and levels of evidence, with 3 to 109 enrolled patients with tongue cancer¹¹. The authors stated the significant role of IOUS in determining the dimensions and margins of the tongue SCC; however, due to large variations in the analyzed publications, they suggest that the reliability of IOUS be proven through prospective and standardized studies. Other publications reported a high correlation of 0.95 between tumor thickness (TT) and DOI measured by intraoperative IOUS and HP reports^{5, 12}. Whether preoperatively or during the surgery, the IOUS exam showed high sensitivity in depicting the dimensions and

deep margins of tongue SCC, which is very important for adequate resection of early-stage carcinomas^{10, 11}. Our prospective study showed a high correlation (0.947) between DOI measurements obtained by IOUS and those in HP reports, almost identical to the cited study¹².

The 8th edition of the staging manual of the AJCC introduces DOI as an independent prognostic factor for oral cavity malignancies⁵. Depth of invasion reflects the proximity of lympho-vascular structures and thus the likelihood of lymph node involvement¹¹. In published literature, for several reasons, the term DOI is often replaced with TT. Upon the definition, TT is the sum of the largest exophytic and endophytic part of the tumor, and DOI is the greatest depth of tissue infiltration by the tumor, measured perpendicular to the line of the surrounding preserved mucosa¹³. A retrospective study by Weimar et al.¹⁴ analyzed T1–T3 stages of OCC and the correlation of TT determined by CT and MRI examination with the HP report. As DOI was not referred to in the majority of HP reports and the overall survival rate was the same whether TT or DOI was measured, the authors concluded that TT may be a surrogate for DOI^{14–16}.

Despite emphasizing DOI as an important prognostic factor in the 8th AJCC tumor, node, metastasis-TNM classification, GD still stands as an indispensable factor in determining the stage of the primary tumor⁵. Our study also analyzed GD, which, although in the prognostic sense, is considered less important relative to DOI and certainly remains a significant factor in planning the operative procedure itself. Additionally, GD is a measure regularly reported in radiology and HP reports; it may also indicate the reliability of the applied imaging modalities in assessing the overall extent of the lesion^{13, 16}. Our results showed the absence of correlation between IOUS and CT measurement of GD with those in the HP report, which illustrates the lower reliability of these techniques in measuring GD. That could be addressed towards the limitation in obtaining GD of irregularly shaped tumors located on movable organs (tongue) or irregularly shaped oral cavity surfaces. Additionally, it can be partly attributed to the errors of subjective assessment of GD. The discrepancy between imaging and HP measurements is also influenced by limiting factors in the pathologist's work¹⁶.

Namely, the processing of tissue in formaldehyde leads to its shrinkage (least for the tongue 91%), and we should not forget the volume variations of the delivered resected tissue, as well as the differences in the direction of cutting the specimen¹⁶.

We excluded OCC where the DOI and GD were not mentioned in the HP report, which is one of the reasons for the small number of patients analyzed in relation to the total number of examined patients (11 out of 52) and, therefore, the main limitation of our study. Our study showed a higher degree of correlation between applied imaging methods and HP in the DOI value compared to a previously published study, but it should be noted that the time interval from diagnostic processing to surgery in all our patients was up to four weeks. Weimar et al.¹⁴ reported a higher (83%) radiological-HP correlation of TT measurements in patients in whom four weeks or less elapsed from CT/MRI examination to surgery, which is close to our CT/HP correlation results. However, the correlation between IOUS and HP measurements of DOI in our study was 95%, which is obviously higher than the CT/MRI correlation^{14, 16}. The mentioned difference can be explained by the proportion of carcinomas on the base of the tongue in the mentioned studies, which were not included in our research.

A meta-analysis of early-stage OCCs showed a correlation of 0.82 between IOUS and HP measurements of TT, which is lower compared to our results (0.947)¹⁷. A recent study from 2020 reported a higher degree of correlation between IOUS and HP measurements of TT/DOI, identical to our results (0.95)¹². Nevertheless, IOUS is a new, operator-dependent diagnostic method with a long learning curve, limited to probe-accessible parts of the oral cavity¹⁸.

A retrospective study from 2021 stated that TT is not a significant prognostic factor for early-stage OCC and that DOI is not an independent and sufficient prognostic factor. Comparing the early OCC staged both with the 7th and 8th editions of the AJCC manual, the authors concluded that according to the 8th edition, upstaging occurred in 23% of cases, which decreased DSS but did not affect PFS. According to their results, different sublocations of OCC should be considered separately due to their specific architecture, lympho-vascular network, possibility of perineural spread, and the

type of infiltrative growth pattern should be taken into consideration as well⁶. In our study, 2 (18.2%) patients had SCC of the lower gingivobuccal sulcus. These buccal SCCs are the most common OCCs in South Asia due to the habit of chewing tobacco and have a greater infiltrative-destructive potential compared to tongue carcinomas⁸. OCCs in the lower gingivobuccal sulcus were accessible to IOUS examination, while for CT examination, it was necessary to apply the inflated cheek technique¹⁹. For adequate CT imaging of OCCs located on the ventral side of the tongue, we modified the proposed maneuvers³. However, in two patients with lateral edge tongue carcinoma, artifacts from dental fillings obscured CT tumor visualization. The 8th edition of the AJCC manual points out that OCC is usually evaluated with CT or MRI but also claims that lesions with a DOI of 4 mm or less may remain unrecognized using these imaging methods⁵. Respecting these facts, the systematic review by Marcello Scotti et al.²⁰ stressed the IOUS as a reliable imaging technique in the evaluation of initial oral cavity lesions.

The limitations of our study are the small sample size and the single-center experience. Strict inclusion criteria that we applied have to be considered, which referred to the initial (clinical T1/T2) tumor lesions, their accessibility to the IOUS examination, as well as to the fact that the values of DOI and GD were stated in the HP report. Although numerous studies have shown a high degree of correlation of IOUS with HP staging of OCC at accessible sites, the retrospective nature of any systematic review does not preclude the need for future prospective studies on the reliability of IOUS compared with other imaging modalities²⁰. Our prospective study supports this view, aiming to present the results of the IOUS application in the evaluation of OCC in Serbia, where, as far as we know, no results have been published yet.

Conclusion

Measurements of DOI obtained by IOUS significantly correlated with those in the HP report, suggesting that IOUS is a reliable tool in the evaluation of small tumors and tumors that cannot be seen on CT examination due to metal dental artifacts. This research emphasizes the role of IOUS in the multimodal diagnostic approach of OCC.

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