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PREOPERATIVE DETERMINATION OF TUMOR THICKNESS IN ORAL SQUAMOUS CELL CARCINOMA BY COMPUTED TOMOGRAPHY

PREOPERATIVNO ODREĐIVANJE DEBLJINE TUMORA ORALNOG SKVAMOCELULARNOG KARCINOMA KOMPJUTERIZOVANOM TOMOGRAFIJOM

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Summary

Introduction. Evaluation of the prognostic factors and the survival rate in oral squamous cell carcinoma is extremely important, because patients in the same tumor-node-metastasis stage may have a different survival rate. Numerous studies have been conducted on various clinical and pathological prognostic factors in order to develop a prognostic model for the survival rate of patients with oral cancer. **Material and Methods.** The study was designed as a prospective study including 65 consecutive patients (n = 65) of both sexes who underwent surgical treatment of oral cancer. The diagnosis of oral cancer was based on the medical history, physical examination, and biopsy. The clinical tumor-node-metastasis staging was determined based on clinical examination. The radiological tumor-node-metastasis staging was done by computed tomography of the head, neck, and chest. The tumor thickness was determined by computed tomography and histopathological analysis of surgical specimens. **Results.** The histopathological analysis showed a mean tumor thickness of 13.446 mm, while the mean computed tomography tumor thickness was 15.2707 mm. The correlation between computed tomography tumor thickness and histopathological tumor thickness was moderately significant (Spearman's rho=.581, p =0.000). **Conclusion.** This study supports the use of computed tomography in the determination of tumor thickness in patients with oral squamous cell carcinoma. We want to emphasize the importance of preoperative, detailed imaging evaluation of patients in order to avoid multiple surgical procedures, significant morbidity, and unnecessary costs.

Key words: Carcinoma, Squamous Cell; Tomography, X-Ray Computed; Preoperative Period; Mouth Neoplasms; Prognosis; Survival Rate

Sažetak

Uvod. Poznavanje prognostičkih faktora stope preživljavanja kod oralnog skvamoznog karcinoma je od izuzetnog značaja jer pacijenti u istom tumor-čvor-metastaza stadijumu bolesti mogu imati različitu stopu preživljavanja. Sprovedene su brojne studije o različitim kliničkim i patološkim prognostičkim faktorima u cilju razvoja prognostičkog modela stope preživljavanja pacijenata sa oralnim karcinomom. **Materijal i metode.** Studija je osmišljena kao prospektivna i obuhvatila je 65 uzastopnih pacijenata (n = 65) oba pola koji su imali hirurški tretman za oralni karcinom. Dijagnoza karcinoma usne šupljine postavljena je na osnovu anamneze, fizičkog pregleda i biopsije. Klinički tumor-čvor-metastaza stadijum utvrđen je na osnovu kliničkog pregleda. Radiološki tumor-čvor-metastaza stadijum uključivao je pregled kompjuterskom tomografijom glave, vrata i grudnog koša pacijenta. Debljina tumora je određena kompjuterizovanom tomografijom i patohistološkim merenjem na postoperativnom uzorku tumora. **Rezultati.** Prosečna debljina tumora na patohistološkom preparatu bila je 13,446 mm, dok je prosečna debljina tumora kod pregleda kompjuterskom tomografijom bila 15,2707 mm. Korelacija između debljine izmerene kompjuterskom tomografijom i postoperativne debljine bila je umereno značajna (*Spearman rho* = 581, P =0,000). **Zaključak.** Ova studija podržava ulogu kompjuterske tomografije u određivanju debljine tumora kod pacijenata sa oralnim skvamocelularnim karcinomom. Želimo da istaknemo važnost preoperativne, detaljne slikovne evaluacije pacijenta kako bi se izbegli višestruki hirurški zahvati, značajan morbiditet i nepotrebni troškovi.

Ključne reči: skvamocelularni karcinom; CT; preoperativni period; oralne neoplazme; prognoza; stopa preživljavanja

Introduction

Oral squamous cell carcinoma (OSCC) is the 8th most common malignancy in the world. More than 177,000 people die annually from oral cancer [1]. Evaluation of the prognostic factors and the survival rate in OSCC is extremely important, because patients in the same tumor-node-metastasis (TNM) stage may have a different survival rate. Numerous studies have been conducted on various clinical and pathological prognostic factors in order to develop a prognostic model of the survival rate of patients with oral cancer [2]. The presence of nodal cervical metastasis is certainly the most significant prognostic factor; however, the presence of occult cervical metastasis represents a therapeutic problem for OSCC since it is present in 18 - 53% of patients with T1-2 N0 OSCC, therefore, the prediction of the nodal change is of great importance [3].

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Abbreviations

TNM – tumor-node-metastasis
OSCC – oral squamous cell carcinoma
SCC – squamous cell carcinoma
CT – computed tomography
TT – tumor thickness
HP – histopathological
NMR – nuclear magnetic resonance
MRI – magnetic resonance imaging

Current diagnostic methods are insufficiently sensitive in detecting occult nodal metastasis, which is why many patients with T1-2 N0 OSCC undergo elective neck dissection which can represent an overtreatment in patients without nodal cervical metastasis [4]. Tumor thickness (TT), compared with melanoma treatment, is increasingly used as a predictor of cervical nodal metastasis in OSCC [5]. It is measured by default on postoperative pathological specimens, but preoperative determination of TT would be very useful to avoid two-step surgery or overtreatment. Different diagnostic techniques were used for preoperative determination of TT and conflicting results were obtained [4, 5].

The aim of this study was to evaluate the use of computed tomography (CT) in preoperative determination of TT in OSCC.

Material and Methods

The study was designed as a prospective study including 65 consecutive patients (n = 65) of both sexes who underwent surgical treatment of oral cancer at the Clinic of Maxillofacial and Oral Surgery of the Clinical Center of Vojvodina, from January 2013 to December 2015. All the patients signed an informed consent for all the examinations and treatment conducted during the study. The diagnosis of oral cancer was based on the medical history, physical examination, and biopsy. According to the localization of the tumor in the oral cavity, patients were divided into five groups: tumors on the tongue, on the floor of the mouth, on the hard palate, on the gingiva, and on the buccal mucosa. The TNM cancer staging was based on clinical examination. The radiological TNM cancer staging was done by CT of the head, neck, and chest, which provided reliable data about the tumor size. The patients with lung metastasis were excluded from the study. After obtaining clinical findings and CT results, the patients' treatment was planned based on their TNM status. The TT was measured on the coronal CT scans **(Figure 1a)**. The surgically resected tumor specimens were fixed on the surface of polystyrene and marked according to the localization in the mouth and according to the regions of the neck of the neck samples. After measuring tumor diameters, they were fixed with formalin and embedded in paraffin. The tissue sections were stained with hematoxylin and eosin. Postoperative pathological examination was performed by the same experienced pathologist. The TT was determined by CT examination and by the pathologist performing the postoperative histopathological (HP) analysis **(Figure 1b)**.

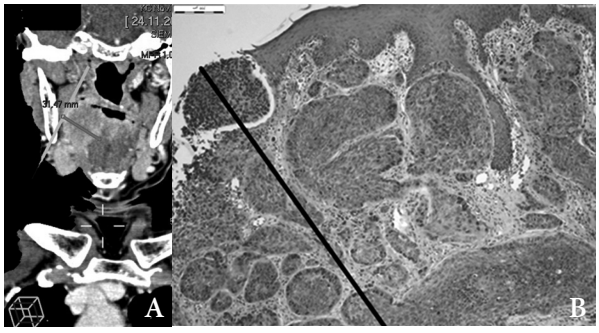


Figure 1. Determination of TT in OSCC by CT (A) and HP measurements (B)
Slika 1. *Određivanje debljine tumora oralnog skvamocelularnog karcinoma korišćenjem kompjuterizovane tomografije (A) i patohistološkim merenjem (B)*

The statistical analysis of the collected data was performed by using appropriate methods. Variables were summarized by descriptive statistics. Mean, median, standard deviation, minimum and maximum values were computed for numerical variables, while categorical variables were summarized by percentages. Normality of variables was tested by the Shapiro Wilk test. Bland-Altman plot was used to validate the agreement between two variables. To access linear relationship between variables, correlation analysis and linear regression were performed. All tests were conducted with a statistical significance level of $p < 0.05$. The IBM SPSS 20 software was used for quantitative data analysis.

Results

In total, 65 patients were included in the study. The median age was 59.65 years (range 38 - 84). There were 12 females (18%) and 53 (82%) males. Alcohol consumption was reported by 69% of patients. Regarding smoking habits, 17% of patients were non-smokers, and 83% were smokers. The pathologically positive nodal disease was reported in 41.2%. Clinical stages I, II, III, and IVa and IVb were reported in 9%, 26%, 23%, 22%, and 20%, respectively. The mean follow-up duration was 36.2 months (± standard error 4.7). Overall, 25.1% of patients died from any cause in this cohort. In 32 patients the primary tumor localized on the tongue, 22 on the floor of the mouth, in 4 on the hard palate, in 4 on the gingiva, and in 3 on the buccal mucosa.

Tumor thickness - pathological and radiological correlation

The mean postoperative final pathological TT was 1.345 cm while the mean CT TT was 1.527 cm. Relevant descriptive measures are provided in **Table 1.**

The relationship between CT thickness and HP thickness was positive, moderately correlated and statistically significant **(Table 2, Graph 1)**.

Next, a regression model was built with CT TT as predictor of HP TT **(Table 3)**. The model is adequate and it confirms that CT TT can predict HP TT. Results show that explanation of models is 30%. According to the results, higher CT TT increases HP TT.

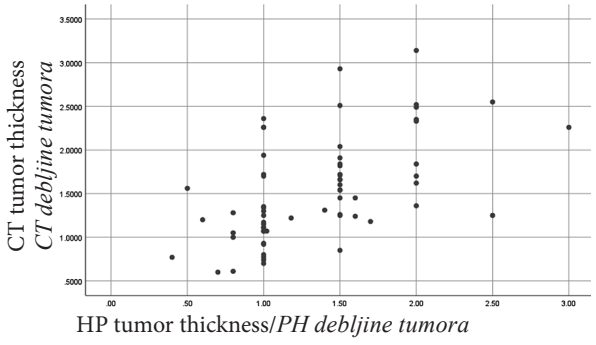
Table 1. Parameters obtained by computed tomography (CT) and histopathology (HP)
Tabela 1. *Parametri određeni kompjuterizovanom tomografijom (CT) i na osnovu patohistoloških merenja (PH)*

	No. *Br.*	Minimum *Minimum*	Maximum *Maksimum*	Mean *Srednja*	Std. Deviation *Std. devijacija*
CT tumor size A (cm)/*CT dimenzija A (cm)*	65	1.5000	8.0000	3.543077	1.0414787
CT tumor size B (cm)/*CT dimenzija B (cm)*	65	1.0000	4.0000	2.095385	.6462466
CT tumor thickness (cm)/*CT debljina tumora (cm)*	65	.6000	3.1400	1.527077	.5834534
Valid N (listwise)/*Validan broj (sa svim podacima)*	65				
	No. *Br.*	Minimum *Minimum*	Maximum *Maksimum*	Mean *Srednja*	Std. Deviation *Std. devijacija*
HP tumor size A/*patohistoloških dimenzija tumora A (cm)*	65	1.0	8.0	3.192	1.4185
HP tumor size B/*patohistoloških dimenzija tumora B (cm)*	65	.2000	7.0000	2.226154	1.0023842
HP tumor thickness/*patohistoloških debljina tumora (cm)*	65	.40	3.00	1.3446	.50704
Valid N (listwise)/*Validan broj (sa svim podacima)*	65				

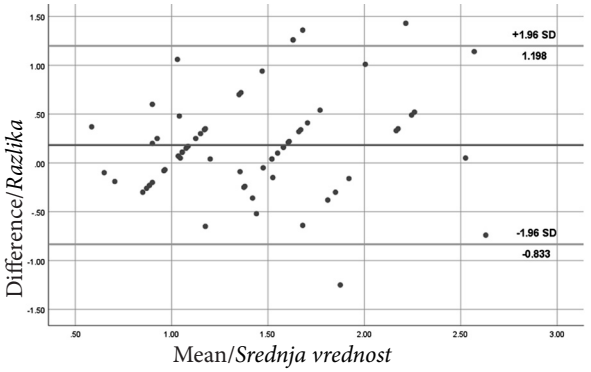
Table 2. Correlation of parameters obtained by computed tomography (CT) and histopathology (HP)
Tabela 2. *Korelacija parametara određenih kompjuterizovanom tomografijom (CT) i na osnovu patohistoloških merenja (PH)*

			CT tumor thickness (cm) *CT debljina tumora (cm)*	HP tumor thickness (cm) *PH debljina tumora (cm)*
Spearman's rho *Spearmanov rho*	CT tumor thickness (cm) *CT debljina tumora (cm)*	Correlation coefficient *Koeficijent korelacije*	1.000	.581**
		p (two-tailed test) *p (dvosmerni test)*	.	.000
		No./*Br.*	65	65
	HP tumor thickness (cm) *PH debljina tumora (cm)*	Correlation Coefficient *Koeficijent korelacije*	.581**	1.000
		p (two-tailed test) *p (dvosmerni test)*	.000	.
		No./*Br.*	65	65

Legend: **Correlation is significant at the 0.01 level (two-tailed)/*Legenda*: ** *Korelacija je značajna na nivou 0,01 (dvosmerni test)*



Graph 1. Correlation between CT tumor thickness and HP tumor thickness
Grafikon 1. *Korelacija između debljine tumora određene kompjuterizovanom tomografijom i patohistološkim merenjem*



Graph 2. Bland-Altman plot of differences between CT and HP tumor thickness
Grafikon 2. *Blad Altmanov grafikon razlika debljine tumora određene kompjuterizovanom tomografijom i patohistološkim merenjem*

The Bland-Altman, i.e. mean-difference or limits of agreement, plot to compare CT TT and HP TT is shown in **Graph 2**.

Discussion

In order to achieve better classification of patients with OSCC and develop a system for prediction of occult cervical metastases, different qualitative and quantitative parameters that describe the tumor itself are used, and one of them is TT. For surgeons, preoperative determination of TT is very important, so that they can plan surgical therapy and avoid two-step surgery. To date, preoperative establishment of TT has never become a standard procedure. Several methods have

Table 3. Regression model
Tabela 3. *Regresioni model*

R = 0.556; R^2 = 0.309; MS = 5.083; F = 28.164; df = 54; p = 0.001					
Model/*Model*	Unstandardized coefficients *Nestandardizovani koeficijent*		Standardized coefficients *Standardizovani koeficijent*	t	p/*p*
	B/*B*	Std. error/*Std. greška*	Beta/*Beta*		
1 Constant/*Konstanta*	0.607	0.149		4.084	.000
CT tumor thickness/*debljina tumora određena kompjuterizovanom tomografijom (cm)*	0.483	0.091	0.556	5.307	.000

Dependent variable: HP tumor thickness (cm)/*Zavisna varijabla: patohistološka debljina tumora*

been investigated: intraoral ultrasonography, nuclear magnetic resonance (NMR), and CT imaging.

Intraoral ultrasonography is used for predicting preoperative TT. Kodama et al. measured TT intraoperatively using intraoral ultrasound in 13 patients with biopsy-proven OSCC of the tongue [6]. They also marked the parts which were 1cm from the greatest thickness of tumor invasion with needles in order to determine the precise surgical margins. The Pearson's correlation test was used to compare ultrasound and HP measured TT, and a high degree of correlation was found, namely 91.4 - 98.2%. Intraoperative ultrasound of the tongue has been proven to be very reliable for determination of tissue characteristics and depth of tumor invasion in patients with squamous cell carcinoma (SCC) of the tongue [6].

Shintani et al. described the correlation between preoperatively determined TT by intraoral ultrasound and the pathological postoperative TT in oral tongue carcinoma [7]. The limitations of this method are tenderness, trismus, and anatomical localization which may make it difficult to place the ultrasound probe. In tumors thicker than 20 mm, there was a discrepancy between HP and ultrasound-determined TT both due to the limitation of ultrasound transducers and due to tissue shrinkage during fixation and HP preparation [8, 9].

In addition to intraoral ultrasound, other techniques that may be used for measuring preoperative TT in oral cancer were investigated. One of them is NMR. This technique was also used to measure the thickness of OSCC tumors as a superior technique compared to ultrasound measurement. Lam et al. showed the importance of NMR in determining TT in their study. The study included 18 patients with OSCC located on the tongue that underwent preoperative NMR. The TT obtained on images at T1 and T2 time was compared with TT determined by HP after glossectomy [10]. At both times, the tumor had complementary characteristics with the images obtained by NMR examination. Using the Pearson's correlation test, they found a statistically significant correlation between these two parameters; there was a significant correlation between the value obtained by measuring at T1 time and HP TT (R = 0.938) and concluded that NMR examination of patients with SCC of the tongue could be performed preoperatively to determine TT, and they also recommended this technique for planning surgery in patients with OSCC. Preda et al. examined the correlation between TT measured during NMR examination and HP measured TT in 33 patients with OSCC located on the mobile part of the tongue [11]. They also observed a statistical association between TT and the occurrence of ipsilateral or contralateral nodal cervical metastases. They found a high correlation between TT measured by NMR and TT measured by HP measurement, as well as an association between TT and the occurrence of nodal cervical metastases: they recommended that tumor depth of ≥ 5 mm indicated ipsilateral neck dissection and tongue tumors of ≥ 20 mm indicated bilateral neck dissection [11]. Most of the studies reported in the literature covering the measurement of OSCC TT by NMR examination focus on SCC of the mobile part of the tongue. The NMR is a technique that is superior to CT examination, since it provides excellent soft-tissue resolution, excellent visualization of all structures in the oral cavity, and shows tumor invasion of bones very early, even before CT scan, and the patient is not exposed to radiation as in CT examination. The NMR examination shows more detailed data on the degree of tumor extension as well as on the cervical nodal status in head and neck tumors. Data on a strong correlation between HP TT and TT measured by NMR can be found in the literature [12, 13]. Alsaffar et al. in particular, reported that there was a strong correlation between these two parameters in tumors with a greater thickness. In their study, which included 53 patients with OSCC of the tongue, a strong correlation between radiologically and HP measured TT was found in tumors with thickness ≥ 5 mm, while in tumors less than 5 mm thick, the radiological correlation between clinical and HP TT was weak [14]. The problem about NMR technique is that it is less accessible to healthcare facilities in comparison to ultrasonography or CT, it is more expensive, lasts longer, it is uncomfortable for patients, and cannot be used in case of claustrophobic patients [12, 13]. Therefore, it can be concluded that this technique of measuring OSCC TT cannot yet be enforced as the standard in planning OSCC treatment.

The CT is now believed to be the standard in staging OSCC and this radiological method is now available in almost all health care institutions. Nowadays,

CT is a widely used method for the diagnosis and planning of treatment of patients with OSCC. It is a non-invasive, accessible method that visualizes soft tissues, bones, and blood vessels as well. Also, CT is fast, cost-effective and, unlike magnetic resonance imaging (MRI), patients with implanted medical metal implants can undergo this examination. It lasts shorter than MRI and it is therefore more comfortable for patients. The disadvantage of CT examination is the high dose of radiation, as well as the possibility of allergic reaction to the contrast agent, which may occur in some patients. The CT examination should be avoided in case of severe diabetics or patients with renal impairment, because the contrast agent may impair the renal function. During the CT examination of patients with OSCC, the surgeon obtains information on the size of the tumor, the degree of tumor invasion, the relationship between the tumor and the vascular components, the condition of bones of the upper and lower jaw, and nodal cervical status. In addition to ultrasound and NMR, the literature also mentions the use of CT in determining preoperative TT in patients with oral planocellular carcinoma. The most accurate measurement of TT from its surface to its deepest point can be performed on coronal images and is expressed in mm.

Our data set is comparable to the group of patients analyzed by Madama et al. They included 116 patients treated for OSCC, of whom 50 were women and 66 men. In their study, 27.2% of patients were smokers, while 35.1% were ex-smokers. Of the total number, 41.2% of patients had nodal cervical metastases and in our study 46.15% of patients had nodal cervical metastases. The average TT measured by CT in their study was 12.88 mm, while in our study it was 15.27 mm. The average TT measured by HP measurement in the Madama's study was 11.60 mm, while in our study it was 13.45 mm (1.345 cm). Madama's study showed a statistically highly significant correlation between preoperatively and postoperatively measured TT (Spearman $r = 0.755$, $p < 0.001$) [15].

The estimation of TT by using different imaging methods has not been discussed sufficiently. Authors who have studied this issue have presented different results. The study about utilization of NMR in determination of TT in different oral carcinoma localizations was performed by Park et al. Their study showed a strong correlation between TT measured by NMR and postoperatively on HP specimens of the tongue, tongue base, and tonsil cancers (Pearson's correlation coefficient was 0.949, 0.941, and 0.578) [16]. This study is also significant because it proved the existence of correlation between TT measured by NMR and existence of cervical lymph node metastasis with cut-off values of 9.5 mm and 14.5 mm, respectively [16]. On the other hand, they found that the histological mean TT was less than TT determined by NMR. They explained this result by tissue shrinkage after resection and processing, which was previously reported in the literature [15, 16].

However, Lwin et al. reported contradictory views on this issue. In their study, NMR was used for determination of TT preoperativly, and they concluded that TT measured by NMR could not precisely determine the indication for neck dissection in OSCC. What is interesting is that they reported a total of 11 tumors, from 2 to 24 mm in size, which were clinically evident but immeasurable by NMR [17].

Conclusion

The results of this study support the use of computed tomography in the assessment of tumor thickness in patients with oral squamous cell carcinoma. It is important to emphasize the importance of preoperative detailed imaging evaluation of patients in order to avoid multiple surgical procedures, significant morbidity, and unnecessary costs.

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