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APPLICATION OF THE EIGHTH EDITION OF THE AMERICAN JOINT COMMITTEE ON CANCER STAGING SYSTEM FOR ORAL CARCINOMA

IMPLEMENTACIJA OSMOG IZDANJA SISTEMA STADIRANJA ORALNOG KARCINOMA AMERIČKOG KOMITETA ZA KARCINOM

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Summary

Introduction. Oral squamous cell carcinoma is the sixth most common carcinoma in the world. Annually, it accounts for 5% of all newly discovered cancers. The most important prognostic factor is the stage of the disease. The tumor, node, and metastasis staging system has been the cornerstone for clinical classification of oral squamous cell carcinoma. **Material and Methods.** The study included 65 patients with oral squamous cell carcinoma who underwent surgery at the Clinic of Maxillofacial Surgery of the Clinical Center of Vojvodina in Novi Sad. The tumor, node, and metastasis status was determined according to 7th and 8th edition of the tumor, node, and metastasis classification. **Results.** Statistical differences between the 7th and 8th edition of tumor, node, and metastasis classification were examined. There was also a change in the nodal status; in 20% of patients there was a transition from N1 to N2, as a result of a more precise definition of nodal status in patients with oral carcinoma. **Conclusion.** This research has pointed out the significance of tumor size as a predictive factor in oral squamous cell carcinoma, which indicates the importance of its local control (for surgical and radiological treatment). The 8th edition of the tumor, node, and metastasis classification for oral cavity cancers made a significant shift by clearly defining depth of tumor invasion into the tumor status.

Key words: Mouth Neoplasms; Carcinoma, Squamous Cell; Neoplasm Staging; Prognosis; Neoplasm Invasiveness; Tomography, X-Ray Computed; Predictive Value of Tests; Surgery, Oral

Introduction

Oral squamous cell carcinoma (OSCC) is the sixth most common carcinoma in the world. Annually, oral carcinoma accounts for 5% of all newly diagnosed tumors, and for 14% of all malignant tumors of the head and neck [1]. In developing countries, oral carcinoma is the third most common carcinoma, after colorectal and cervical carcinoma (Sri Lanka, India, Pakistan,

Sažetak

Uvod. Oralni planocelularni karcinom je po učestalosti šesti maligni tumor u svetu. Godišnje oko 5% svih novootkrivenih tumora pripada ovom malignom tumoru. Najvažniji prognostički faktor je stadijum bolesti. Postojeći sistem stadiranja koji uključuje veličinu tumora, nodalni status postojanje udaljenih metastaza je kamen temeljac klasifikacije po kliničkim stadijumima oralnog planocelularnog karcinoma. **Materijal i metode.** Istraživanje je uključilo 65 bolesnika sa oralnim planocelularnim karcinomom koji su lečeni na Klinici za maksilofacijalnu hirurgiju Kliničkog centra Vojvodine u Novom Sadu. Status tumora je određen na osnovu sedmog i osmog izdanja klasifikacije karcinoma Američkog komiteta za karcinom. **Rezultati.** Uočeno je postojanje statistički značajne razlike između sedmog i osmog izdanja kriterijuma za određivanje stadijuma oralnih planocelularnih karcinoma. Postojale su promene i u nodalnom statusu, kod 20% bolesnika uočen je prelaz iz N 1 u N 2 stadijum kao rezultat preciznije definicije N-statusa kod bolesnika sa oralnim karcinomom. **Zaključak.** Istraživanje je pokazalo značaj dimenzije tumora kao prediktivnog faktora kod planocelularnih oralnih karcinoma, čime se naglašava značaj lokalne kontrole kod lečenja oralnog planocelularnog karcinoma tokom hirurškog i radiološkog tretmana. Osmo izdanje klasifikacije za tumore oralne regije dovelo je do značajnih promena uvođenjem dubine invazije u T-status.

Glavne reči: neoplazme usta; skvamozni karcinom; stadiranje neoplazmi; prognoza; invazivnost neoplazmi; CT; prediktivna vrednost testova; oralna hirurgija

Bangladesh, and Brazil). In some parts of India, oral carcinoma accounts for almost 50% of all malignant tumors. In developed countries, this type of malignant tumor is somewhat less common [1]. It is estimated that this malignant tumor is the 8th most common carcinoma in Europe, although these data vary in relation to the country. The highest incidence of oral carcinoma in Europe is in the Central and Eastern Europe, especially in Hungary, Slovakia and northern France. Not

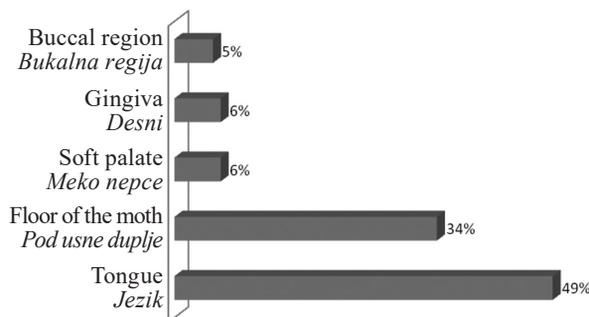
Abbreviations

OSCC	– oral squamous cell carcinoma
TNM	– tumor, node, and metastasis
HPV	– human papillomavirus
AJCC	– American Joint Committee on Cancer
DTI	– depth of tumor invasion
CT	– computed tomography
UICC	– Union for International Cancer Control

enough attention has been paid to oral carcinoma, although around 200,000 people are diagnosed annually in the world. According to Globocan data, there were 354.854 newly discovered and registered patients in 2018, 726 in Serbia. The OSCC more commonly affects males than females (male : female ratio is 3 : 1), which is explained by a higher percentage of risky behaviors in men rather than in women. The main etiological factors for the development of oral planocellular carcinoma are smoking and alcohol consumption. These factors act independently as well as synergistically. Poor oral hygiene, inadequate prosthetic restraint, genetic malformations, malnutrition, hypovitaminosis, human papillomavirus (HPV) infections are also etiological factors affecting the development of OSCC [2]. The most common localization of OSCC is the mucosa of the tongue (20 – 40%) and floor of the mouth (15 – 20%), while other localizations of the oral region are affected by a significantly smaller percentage. The average five-year survival of patients is 50% [1, 3]. According to research, African American people have slightly worse five-year survival than Caucasians. The most important prognostic factor is the stage of the disease. The tumor, node, and metastasis (TNM) staging system has been the cornerstone for clinical classification of OSCC. The system itself had drawbacks; it was considered to have low prognostic value especially in the early tumor stage. The 8th edition of TNM staging system used by the American Joint Committee on Cancer (AJCC) brings many changes especially in T status by incorporating of depth of invasion (DTI) in the T category. The aim of this study was to verify the differences in classification of patients according to older 7th and newer 8th TNM classification.

Material and Methods

The study included 65 patients with OSCC who underwent surgery at the Clinic of Maxillofacial Surgery of the Clinical Center of Vojvodina in Novi Sad in the period January 1, 2015 – December 31, 2018. The diagnosis of OSCC was based on medical history, clinical examination and punch biopsies. After pathohistological confirmation of OSCC, the patients were examined by computed tomography (CT) of the head, neck and chest at the Clinic of Radiology of the Clinical Center of Vojvodina. The CT scans were made according to the protocol for CT examination of the head, neck and chest. The patients were operated under general anesthesia. The TNM stage was based on both CT scans and pathohistological findings. The pathological TNM status was determined according to the 7th and 8th editions of the TNM classification. Furthermore, the statistically sig-



Graph 1. Localization of the oral squamous cell carcinoma (No = 65)

Grafikon 1. Lokalizacija oralnog planocelularnog karcinoma (Br. = 65)

nificant differences between the 7th and 8th edition of TNM classification were examined. The χ^2 test was used with a statistical significance of $p < 0.05$.

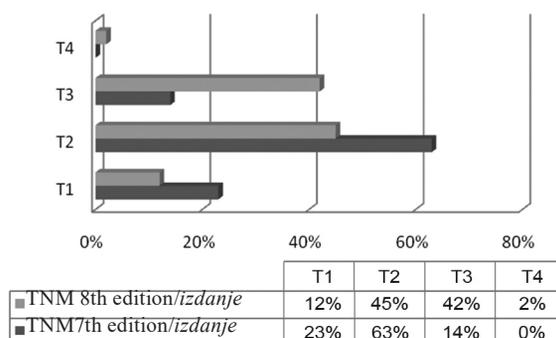
Results

Patients' characteristics

Out of 65 patients, the majority were male (82%) and the average age was 59.65 years (SD \pm 9.425). The youngest patient was 38 years old and the oldest 84. Almost half of the subjects had a tumor localized in the mucosa of the tongue and floor of the mouth (**Graph 1**). Around 83% of patients were smokers (38% smoked 30 cigarettes per day over 30 years), while 67% of patients regularly consumed alcohol.

TNM classification of OSCC

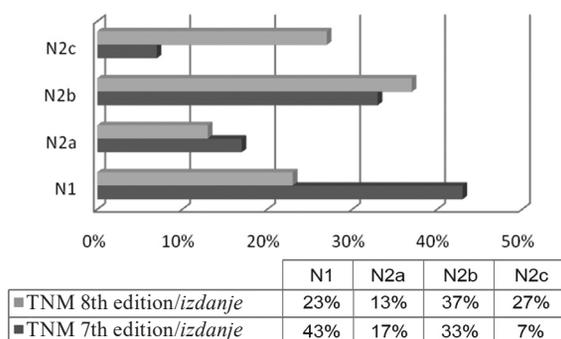
Following histological verification of oral OSCC and CT of the head, neck and chest, all patients were operated under general anesthesia. The tumor excision with resection of the lower jaw and the appropriate dissection of the neck was made, depending on the radiological N status. Pathological TNM status was determined according to the 7th and 8th editions of the TNM classification (**Graphs 2 and 3**). Subsequently,



Graph 2. Changes in the T status of the examined patients (No = 65)

Grafikon 2. Promene u T-statusu u uzorku (Br. = 65)

Legenda: TNM - tumor, nodus i metastaze



Graph 3. Changes in the N status of the examined patients (No = 65)

Grafikon 3. Razlike u N-statusu u uzorku (Br. = 65)

Legenda: TNM - tumor, nodus i metastaze

both T and N categories were compared using these two editions of the TNM classification.

There was a statistically significant difference in the T status between the 7th and 8th editions of TNM classification ($Z = -3.921, p = 0.000$). In 51% of patients, the T status remained the same, in 42% of patients the T category has increased, while in 8% of patients the T category has decreased. The main reason for changes in T status is implementation of the depth of tumor invasion in the T status. About 37% of the sample (N = 65) had a depth of tumor invasion of 5 – 10 mm, and in 40% the depth was over 10 mm (Graph 4).

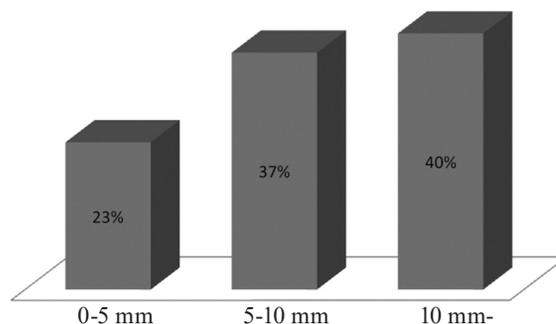
There was also a change in the N status; in 20% of patients there was a transition from N1 to N2 category as a result of a more precise definition of N status in patients with oral carcinoma in the 8th edition.

Discussion

The TNM classification of malignant tumors is a cancer staging system developed by Professor Pierre Denoix in the period between 1943 and 1952, which analyzes the size and extent of the primary tumor, the presence of regional lymph node metastases and the presence of distant metastases. The system itself is mostly developed by the Union for International Cancer Control (UICC) in order to establish consensus and standards for the classification of malignant tumors, as well as the AJCC. The UICC and AJCC classification systems were unified in 1987, as a unique TNM system for the classification of malignant tumors [4]. This classification system is used for staging malignant tumors, assessing the response to malignant tumor therapy and analyzing survival. The TNM system describes the malignant tumor stage by an alphanumeric code, describing the three most significant characteristics of malignant tumors [4, 5].

T (TX - T4) stage describes the size and extent of the tumor.

N (NX - N3) stage describes the number and size of lymph node metastasis.



Graph 4. Distribution of the patients according to the depth of tumor invasion (No = 65)

Grafikon 4. Raspodela bolesnika prema dubini invazije tumora (Br. = 65)

M (M0 - M1) stage describes the presence or absence of distant metastases.

In addition to these three most important characteristics in the TNM classification, the following tumor characteristics are included:

- G (1 - 4) degree of tumor cell differentiation
- S (0 - 3) serum tumor marker level
- R (0 - 2) radicalism of surgical tumor excision
- L (0 - 1) invasion of lymph vessels
- V (0 - 2) vein invasion (microscopic, macroscopic)
- C (1 - 5) reliability modifier of specific parameters.

During guidance on the TNM staging, the following prefixes are used to describe the stage of malignant tumors even more accurately:

- c prefix indicates the TNM stage determined by a clinical examination of the patient;
- p prefix indicates the TNM stage described after the pathohistological examination of the preparation
- y prefix indicates the TNM stage after chemotherapy, radiotherapy or neoadjuvant therapy;
- r prefix indicates the TNM stage in recurrent malignant tumors;
- a prefix indicates the TNM stage after autopsy;
- u prefix indicates the TNM stage determined by ultrasound.

Today, the TNM classification system is used worldwide for staging most primary malignant tumors and carcinomas, but cannot be used in diffuse malignancies such as leukemia. Its use in staging diffuse lymphoma and ovarian carcinoma is also very limited. It should be emphasized that this system has changed and improved over time with the development of technology, new precise diagnostic methods, new biological discoveries and treatment of malignant tumors. So far, AJCC has published 8 revisions of the TNM classification of malignant tumors. Since 2018, the 8th revision of TNM tumor classification has been used. The greatest difference between the 7th and 8th editions of the TNM classification for oral carcinomas is in T status: in the new 8th edition, the T0 status has been removed, while in T1, T2 and T3, the depth of tumor invasion is included as a classification parameter [6]. In this study, when the TNM status was determined in pa-

Table 1. Differences in T status between 7th and 8th edition of TNM classification for oral carcinoma
Tabela 1. Razlike u T-stadijumu između sedmog i osmog izdanja TNM statusa oralnog karcinoma

TNM 7 th edition from 2010/TNM 7. izdanje 2010. godina	TNM 8 th edition from 2018/TNM 8. izdanje 2018. godina
T0 - no primary tumor/T0 - nema primarnog tumora	T0 – removed/T0 je uklonjeno
T1 - tumor ≤ 2 cm T1 - tumor ≤ 2 cm	T1- tumor ≤ 2 cm or DIT ≤ 5 mm T1- tumor ≤ 2 cm ili dubina invazije ≤ 5 mm
T2 - tumor size 2 – 4 cm T2 - tumor veličine 2-4 cm	T2 - tumor ≤ 2 cm with DIT 5 – 10 mm or tumor size 2 - 4cm with DIT ≤ 10 mm T2- tumor ≤ 2 cm sa dubinom invazije 5-10 mm ili tumor veličine 2-4 cm sa dubinom invazije ≤10 mm
T3 - tumor greater than 4 cm T3 - tumor veći od 4 cm	T3 - tumor greater than 4 cm or DIT ≥ 10 mm T3 - tumor veći od 4 cm ili dubina invazije ≥ 10 mm
T4 T4a - moderately advanced tumor with infiltration of the extrinsic muscle of the tongue/T4a umeren uznaredovali tumor infiltracija ekstrinzičkih mišića jezika T4b - advanced tumor/T4b - uznapredovali tumor	T4a - infiltration of extrinsic muscle of the tongue is excluded, implying invasion of the cortical bone and surrounding tissue as well as the maxillary sinus/T4a - isključena infiltracija ekstrinzičkih mišića jezika, podrazumeva invaziju kortikalne kosti i okolnog tkiva kao i maksilarnog sinusa T4b - advanced tumor/T4b - uznapredovali tumor

Legenda: TNM - tumor, nodus i metastaze

Table 2. Differences in N status between 7th and 8th edition of TNM classification for oral carcinoma
Tabela 2. Razlike u N-stadijumu između sedmog i osmog izdanja TNM statusa oralnog karcinoma

TNM 7 th edition of 2010/TNM 7. izdanje 2010. godina	TNM 8 th edition of 2018/TNM 8. izdanje 2018. godina
N0 – no invaded lymph nodes N0 – nema invadiranih limfnih čvorova	N0 – no invaded lymph nodes N0 – nema invadiranih limfnih čvorova
N1 – one invaded ipsilateral lymph node ≤ 3 cm N1 – jedan invadiran ipsilateralni limfni čvor ≤ 3 cm	N1 – one invaded ipsilateral lymph node ≤ 3 cm N1 – jedan invadiran ipsilateralni limfni čvor ≤ 3 cm
N2a – one invaded ipsilateral lymph node 3 – 6 cm N2a – jedan invadirani ipsilateralni limfni čvor 3-6 cm N2b – multiple invaded ipsilateral lymph nodes ≤ 6 cm N2b – multipli invadirani ipsilateralni limfni čvorovi ≤6 cm N2c – ipsi- or contralateral invaded lymph nodes ≤ 6 cm N2c – ipsi ili kontralateralni invadirani limfni čvorovi ≤ 6 cm	N2a – metastases in one ipsilateral lymph node > 3 cm but ≤ 6 cm in the largest diameter without extranodal spread or metastases in one lymph node < 3 cm with extranodal spread/N2a – metastaza u jednom ipsilateralnom limfnom čvoru > 3 cm ali ≤ 6 cm u najvećem dijametri bez ekstranodalnog širenja ili metastaza u jednom limfnom čvoru < 3 cm sa ekstranodalnim širenjem N2b – ipsilateral multiple metastases in the lymph nodes > 6 cm in the largest diathesis without extranodal spread/N2b – ipsilateralne multiple metastaze u limfnim čvorovima > 6 cm u najvećem dijametri bez ekstranodalnog širenja N2c – bilateral or contralateral metastatic altered lymph nodes > 6 cm in the largest diameter without extranodal spread/N2c – bilateralni ili kontralateralni metastatski izmenjenim limfni čvorovi > 6 cm u najvećem dijametri bez ekstranodalnog širenja
N3 – any invaded lymph node > 6 cm N3 – bilo koji invadirani limfni čvor > 6 cm	N3a – metastasis in the lymph node > 6 cm in the largest diameter without extranodal spread N3a – metastaza u limfnom čvoru > 6 cm u najvećem dijametri bez ekstranodalnog širenja N3b – metastases in the lymph node > 3 cm with extranodal expansion, multiple ipsilateral, contralateral and bilateral metastases in lymph nodes with extranodal spread or one contralateral metsatasis in the lymph node less than 3 cm in size with extranodal spread N3b – metastaza u limfnom čvoru > 3cm sa ekstranodalnim širenjem, multiple ipsilateralne, kontralateralne i bilateralne metastaze u limfnim čvorovima sa ekstranodalnim širenjem ili jedna kontralateralna metastaza u limfnim čvoru manja od 3 cm sa ekstranodalnim širenjem

Legenda: TNM - tumor, nodus i metastaze

tients with OSCC, the first TNM was determined according to the 7th edition of the TNM classification (since the research took place in 2016 when the 7th edition of the TNM classification was valid). The second TNM was determined according to the 8th edition, after it was published. The largest changes were recorded in T status, with 49% of patients experiencing a change in T status with a transition to a higher T status (42% of patients). This change in T status was statistically significant ($Z = -3.921$, $p = 0.000$) and was a result of a more precise definition of the pathological T status and the introduction of new quantitative characteristics. In addition to the macroscopic measurement, the depth of tumor invasion is included as an important characteristic in T1, T2 and T3 stage of the 8th edition of the TNM classification from 2018 (**Table 1**). According to the 8th edition of the TNM classification (TNM from 2010 and 2018), the highest percentage of patients in the study had T2 (45%) and T3 (42%) stage of tumor size. The depth of invasion (DI) defines tumor extensions below the surface of the epithelium that indicates a vertical invasion of the tumor from the level of the basal membrane of intact mucosa to the site of the greatest depth of tumor invasion [6, 7]. The interesting fact about this measuring technique is that it can cause practically 'thinner' ulcerous tumors to have a greater depth of invasion, since the DOI is measured from the level of the basal membrane of the intact mucous membrane. In this case, the DOI is greater than the thickness of the tumor [8, 9].

The implementation of the DTI at T status has led to more precise definition of T status of oral squamous cell carcinoma (**Table 1**). In addition to the T status changes, the new, 8th edition of the TNM classification of oral carcinoma has brought changes in the N status [10, 11]. A qualitative category of presence or absence of extranodal spread has been introduced (**Table 2**), in addition to already existing quantitative categories of the number and size of invaded

lymph nodes [12, 13]. Also, the N3 category is divided into three subcategories. The changes were recorded in tested samples in the N status; 20% of patients who according to TNM classification from 2010 had N1 status, according to the TNM classification from 2018 had N2 status [14]. The main reason is the inclusion of extranodal propagation as one of the characteristics of the N status (**Table 2**) [15].

Conclusion

This study has shown the significance of tumor dimension as a predictive factor in oral squamous cell carcinoma, which indicates the importance of its local control (for surgical and radiological treatment). In recent years, the phenotypic and biological differences of primary tumors have been studied in patients with cervical nodal metastases and in those who did not have symptoms of metastatic cancer because of different responses of tumor cells to therapies with regard to tumor microenvironment. It is believed that the characteristics of the metastatic lymph nodes may be an independent prognostic survival factor, such as the presence of distant metastases. This opens the door to new research in defining the metastasis cascade and parameters significant for the survival of patients suffering from oral squamous cell carcinoma. All these investigations leave room for new revisions of the tumor classification and the introduction of new parameters that are significant predictive factors, both in T and N status of the tumor, node, and metastasis classification. The 8th edition of the tumor, node, and metastasis classification system for tumors of the oral region made a significant shift by more clearly defining depth of tumor invasion in the T status. Future revisions will most likely include some other biological and dimensional characteristics of tumors in the T status, in order to more precisely determine the status itself and therapeutic and predictive potentials.

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