RADIOLOGICAL DIAGNOSIS OF MALIGNANT TUMORS OF THE ORAL CAVITY

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The oral cavity and oropharynx represent the topmost parts of the digestive tract, which is unique due to both its complex anatomy and tissue structures localized in a small area. In the head and neck region, oral carcinomas are characterized by high prevalence and mortality, multifactorial etiology and delayed diagnosis. Their prognosis, as in other tumors, depends on the disease stage. More than 90% of the mouth and oropharynx malignant tumors are histopathologically diagnosed as squamous cell carcinomas. Their clinical diagnosis is based on the inspection and palpation, and cranial nerve neurological examinations. The use of computerized tomography (CT) and magnetic resonance imaging (MRI) is a key step in the staging of oral cavity tumors and adequate therapy planning. The knowledge of radiological anatomy and pathology of this region is of great importance in making adequate diagnostic conclusions.

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Introduction

The oral cavity and oropharynx represent the topmost parts of the digestive tract, which is unique due to both its complex anatomy and tissue structures localized in a small area (1). Its main role is food intake, chewing and food preparation for swallowing. Although the sinonasal complex is the main respiratory pathway, the mouth can be considered as a secondary respiratory pathway with a crucial role in phonation. Lip movement allows for different functions such as: speech, coughing and facial expression. The sense of taste is located in the mouth (2).

According to the International classification of diseases and related health problems, tenth revision, issued by the World Health Organization (WHO), oral cavity carcinomas are classified as follows: lip (ex-cluding the skin of the lip), tongue, gum, floor of the mouth, palate and carcinomas of other unspecified parts of the mouth (cheek mucosa, vestibule of the mouth, retromolar area and small salivary glands), excluding carcinoma of the large salivary gland (3). As for the head and neck area, oral cavity carcinomas, characterized by high prevalence and mortality, multifactorial etiology and delayed diagnosis, represent a public health issue, especially in the developing countries (4). Additionally, the treatment of these carcinomas represents a great therapeutic challenge due to poor prognosis of late stage disease, as well as due to the influence of therapeutic treatments on the mouth and pharynx functions.

The oral cavity and pharynx carcinomas are the sixth most frequent malignant tumors worldwide and seventh in Serbia. Their incidence varies with the geographical region. The highest incidence has been found in South Asia, Pacific islands, Latin America and in parts of the Central and Eastern Europe (5).

More than 90% of mouth and oropharynx malignant tumors are histopathologically diagnosed as squamous cell carcinomas (SCCs). Less frequently occurring are the verrucous carcinomas, small salivary gland carcinomas, lymphomas, sarcomas and other malignant neoplasms. According to incidence by regions, squamous cell carcinoma of the oral cavity is the most frequent one, followed by the anterior two thirds of the tongue and floor of the mouth (6).

Clinical evaluation of the oral cavity carcinoma is based on clinical examinations, inspection and palpation, with the addition of the cranial nerve neurological examination. Utilization of computerized

tomography (CT) and magnetic resonance imaging (MRI) represents the main diagnostic procedure in the staging of oral cavity tumors and adequate therapeutic approach planning.

Oral cavity squamous cell carcinoma etiology

Oral cavity SCC etiology is multifactorial and according to the available global evidence, the known risk factors for these tumors could be divided into two main groups: modifiable (risk behavior related) and non-modifiable ones (sociodemographic) (7).

The main etiological factors for the carcinomas of this region are tobacco and alcohol consumption. They can act separately, but their combined influence is boosting the carcinoma incidence, especially if larger amounts are consumed (a large number of cigarettes/alcoholic drinks per day/week) in a prolonged period of time. Moreover, quitting smoking after the initial diagnosis of oral cavity carcinoma and therapy initiation increases survival rates (7).

Recent studies in the USA have revealed a connection between the incidence of orofacial carcinomas and sexually transmitted human papilloma virus (HPV) infection, especially HPV16 (8). The combined analysis of the International head and neck cancer epidemiology consortium (INHANCE) found a correlation between the carcinomas of these regions and risky sexual behavior and HPV infection (9).

The most important non-modifiable etiological factors for the development of oral region carcinomas are low socioeconomic status, age and gender. Oral carcinoma is more frequent in males than in females and around two thirds of all oral cavity carcinomas belong to this type. In parallel, there is an increased risk of this carcinoma in older people, occuring mostly at the age of 50 and over (7,8).

Radiological diagnosis of squamous cell carcinoma of the oral cavity

Early diagnosis of oral cavity carcinoma is a public and health priority, since early discovery contributes to the decrease of mortality and better prognosis during and after treatment.

Although oral cavity SCCs, due to their localization, could be detected by inspection, most of them are discovered in advanced disease stages. Persistent ulcerations and bleeding in the mouth, presence of a mass, swallowing and speech difficulties and ear pain are the most frequent symptoms of oral and oropharyngeal carcinomas. However, some tumors, especially those of the tongue region, can be asymptomatic for a long period of time. Superficial areas with mucosa lesions, such as leukoplakia or erythroplakia, detected at clinical examinations are often the sites with dysplasia or even invasive carcinoma, when the final diagnosis is based on biopsy findings.

Adequate choice of therapy and assessment of disease prognosis involve determination of the grade of the disease. This includes the use of imaging techniques such as CT and MRI. These radiological methods are the ones most frequently utilized, due to their reliability in the estimation of tumor spread, vascular infiltration and metastases to the surrounding tissues. Positron emission tomography (PET) together with the imaging techniques provide combined functional (metabolic) and anatomical information, resulting in a precise diagnosis and a greater chance for improvement of the patient condition (10).

The main advantages of CT compared to MRI are shorter examination period, fast image processing, availability, lesser impact of movement artefacts, and better visualization of destructive bone lesions. Exposure to high x-ray radiation doses, as well as artefacts originating from dental implants, represent the disadvantages of this radiological method.

Depending on CT itself, scan protocols can vary. Native (native-phase) and postcontrast scans are usually performed from the skull base to the top edge of the manubrium (chest bone), with a great capability of image reconstruction. Axial sections at the oral cavity and oropharynx levels should be parallel, while coronal sections should be perpendicular to the hard palate plane. Due to the fact that oral cavity carcinomas are accompanied by tumors of the pharynx, larynx and tracheobronchial tree, the area to be scanned should be expanded to the chest cavity as well (6, 11).

On the other hand, MRI examination allows a better visibility of the soft tissue structures, i.e. tumors, their spread, bone marrow and neurovascular infiltration, especially for the detection of small changes. However, long examination periods, impact of movement artefact, limited access and high cost are the main shortcomings of this method. A high level of cooperation with the patient is needed in order to perform MRI, thus it is not applicable in claustrophobic patients, those with high dyspnea and with metal implants. Standard MRI examination involves the same scan area as in CT, in axial, sagittal and coronal planes. T1W, T2W and STIR, with additional postcontrast T1W with fat suppression and diffusion imaging (DWI) sequences are used. Postcontrast T1W sequence provides the best visualization of tongue tumors, as well as their perineural spreading. Tumor spread to the lateral tongue muscles is best visualized with axial and coronal T2W sequences, in combination with postcontrast sequence. On the other hand, tumor spreading to the bone marrow is best seen using native T1W, STIR and postcontrast T1W sequences. The presence of cancer cells in lymph nodes is estimated using T2W, coronal STIR and postcontrast T1W sequential diffusion (DWI) sequences (11).

When CT is applied, these tumors appear as badly limited areas and with a homogenous density increase after contrast injection. Larger tumors are mostly heterodense due to necrosis.

On T1W MR images tumors appear hypointense or isointense with muscles, whereas on T2W MR images tumors are mostly hyperintense. Solid tumors present as a signal increase after gadolinium contrast application, while the areas of necrosis inside the tumor tissue remain hypointense. Precontrast T1W images are useful for the differentiation between tumor and surrounding fatty tissues, detec-

tion of spread to the bone and neurovascular structures.

Pathways of spread of oral cavity squamous cell carcinoma

Oral SCCs most frequently spread in one of the following three pathways: (a) by direct invasion through the mucosal surface, muscles or bones; (b) by lymph; or (c) by perineural dissemination (12).

a) Direct invasion – initial mucosal spread is best seen during a physical examination. Superficial lesions are radiologically invisible, whereas submucosal and deeper structure dissemination into the fatty and muscle tissues is visible.

The main shortcoming of both of these radiological examinations is low specificity, i.e. one cannot make the difference between tumor tissue and inflammatory changes. Cortical bone invasion is represented as a discontinuation or an erosion with hyperdense edges on CT image or hypointense on all MRI sequences. Subtle cortical bone erosion can be best detected in the bone window during CT examination, while MRI is the most suitable for visual assessment of the extent of medullar invasion. Low signal intensity on native T1W, high intensity on T2W with increased signal intensity after contrast application can correspond to tumor invasion of the bone marrow, but the same image can be seen in inflammation, peritumoral edema and osteomyelitis.

b) Lymphogenic dissemination – large percentage of the oral cavity and oropharynx carcinomas is initially manifested with a change on the neck that corresponds to enlarged lymph nodes, frequently I-III level.

Most of the tumor - affected nodes are enlarged. Nodes with size larger than 1 cm in their transversal shorter diameter, except of those of II level (12 mm), are considered to be pathological. Nodal morphology assessment is also an important criterion. The ratio between longitudinal and transversal nodal diameters is normally higher than two, while pathologically affected nodes are mostly round. Unclear node margins with an increase in the local fatty tissue density on CT examination, and high signal intensity with fat suppression in T2W sequence and postcontrast T1W MRI favor extracapsular spreading. The grouping of three or more border sized lymph nodes in the primary tumor region strongly points to lymph node metastases. Central necrosis represents the most reliable radiological criterion in neck lymph node metastasis diagnostics independent of the tumor size. It is represented as a central hypodense/hypointense area with the edge postcontrast intensity increase.

c) Perineural dissemination – this type of tumor spreading is a characteristic of invasive mouth SCCs and is defined as a malignant cell dissemination via nerve fibers. During CT examination, increased neural opening and surrounding fatty tissue obliteration can be seen. Increase and postcontrast intensification of the nerve and surrounding fat signals is seen on MRI. Muscular denervation atrophy is manifested as a loss of muscle volume and its replacement with fatty tissue.

TNM classification of oral cavity squamous cell carcinoma

Head and neck tumor TNM staging system is an anatomical estimation of the primary tumor spreading, dissemination to the locoregional lymph nodes and the presence of distant metastases. Stage T is defined by the tumor size, depth of invasion and the affected vital structures. In VIIth issue of TNM classification, T4 stage is divided in to T4a and T4b and it depends on the affected vital structure and suitability for surgical treatment. The presence of lymph node metastases (N), their size, number, as well as the presence of extracapsular spreading are the most important prognostic factors for SCC of this region. Distant metastases (M) include the lymph nodes that are affected by tumor tissue cells, except the level VII. Their incidence increases with tumor grade. The most frequent localization of M in carcinomas of this region are the lungs, less frequently the liver and brain (13).

Having in mind that SCC has a different incidence for different regions of the oral cavity and has unique regional spreading patterns, the following text will be dedicated to this topic (6, 12).
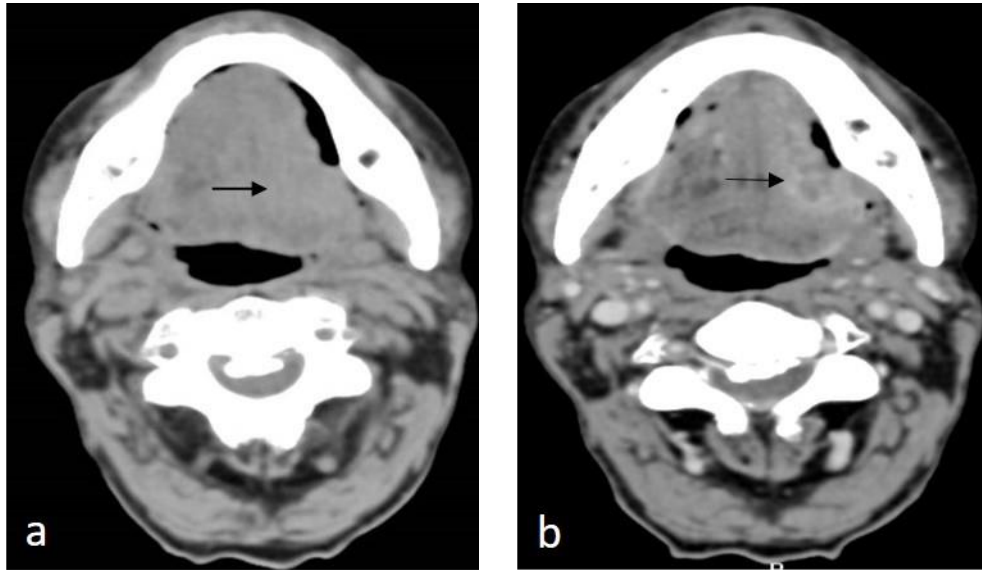
Squamous cell carcinoma of the lip

Mucosal carcinoma, i.e. carcinoma of the inner lip surface is the most common malignant neoplasm of this region, representing 40% of all oral cavity SCCs. The lower lip is predominantly affected, between the middle line and labial commissure, while the upper one is rarely affected. There are three morphological types: exophytic, ulcerative and verrucous. These tumors slowly progress, with rare regional lymph node metastases occuring much later compared to other oral cavity carcinomas. More than a half of patients during the initial radiological examination has a tumor mass larger than 1.5 cm. Native CT and MRI examinations of patients with these tumors show a tumor mass with undefined margins with or without an area of ulceration, while the postcontrast image reveals variable density/signal intensity increase. In the beginning, bone erosion could most frequently be seen at the alveolar ridge region in the bone window during CT examination. Larger tumors could affect the mandible or the mental nerve directly, infiltrate the skin and subcutaneous fatty tissue of the buccal region, floor of the mouth and masticatory space.

Squamous cell carcinoma of the oral part of the tongue

This type of carcinoma commonly originates from the lateral edge of the middle 1/3 of the tongue or from the ventral side and its prognosis is generally better compared to the same tumor of the tongue base which has a lower histological degree of differentiation (Figure 1). Infiltrative, ulcerative or exophytic growth forms can be seen, while most often it is clinically manifested when its dimensions are higher than 2 cm, with the presence of enlarged lymph nodes of the I and II level. Infiltrative carcinomas initially affect lateral tongue muscles (hyo-

glossus, palatoglossus and styloglossus) and spread towards the medial part of the tongue, affecting the genioglossal muscle and lingual septum, ending at the contralateral side. Large tumors arising from the lateral tongue edge can spread towards the tonsillar sulcus, tonsillar fossa, base of the tongue, floor of the mouth, mandible and submandibular spaces, while those from the ventral side spread directly to the floor of the mouth or the base of the tongue. In addition to the standard axial view, the coronal and sagittal MR views are of greater help here, since they give more information concerning the lesion size as well as the state of the neurovascular structures. Perineural spreading along the lingual nerve is responsible for the pain sensations in the ipsilateral ear in patients in the advanced stages.

Figure 1. Squamous cell carcinoma of the tongue, native (a) and postcontrast (b)*

*Native axial CT image, with the presence of a homogenous tumor mass of the left tongue half (arrow) asymmetrically compared to the right side (a). Axial CT image where the increase of postcontrast density of the left tongue half (arrow) can be seen corresponding to the tumorous mass (b).

Squamous cell carcinoma of the floor of the mouth

This type of tumor originates from the mucosa that overlays the space between the gums of the lower jaw and the bottom side of the tongue. Most of the tumors are found on the anterior part of the mouth floor. In the beginning, the lesion is very small, while with the progress characteristic papillary or exophytic formation, spreading in different directions, can be found. Often one of the first disease manifestations is the consequence of direct spreading of the tumor, causing the obstruction of the Warthon's duct and submandibular gland sialadenitis. Tumor spreads in both superior and posterior directions affecting the anterior surface and the base of the tongue, as well as to other neurovascular structures. In the anterior and lateral directions, SCC spreads to the gingival mucosa, mandible and medial pterygoid muscle. In the advanced stages, the process can expand outside the oral cavity, most fre-quently to the parapharyngeal and masticator spaces. Regional I and II level lymph node metastases, predominantly unilateral, occur later compared to the metastases of SCC of the tongue.
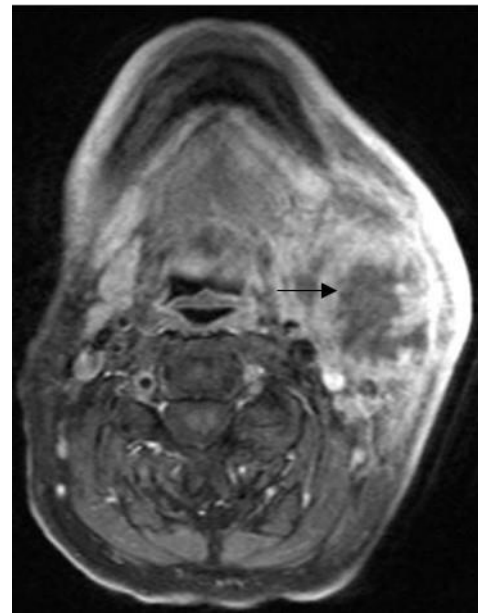
Squamous cell carcinoma of the retromolar triangle

Although this is a small region of the mouth, covered with mucosa and located behind the last molar in the mandibular ramus, retromolar triangle represents a crossroads between the oral cavity, oropharynx, soft palate, buccal space, floor of the mouth, masticator and parapharyngeal spaces. Carcinoma of this location can spread to some of the surrounding structures (Figures 2 and 3), including the tonsils, base of the tongue, to the temporal muscle via pterygomandibular raphe, medial to the pterygomandibular space, in the inferior and anterior direction to the floor of the mouth and pterygo-palatine fossa, respectively.

Figure 2. Squamous cell carcinoma of the mandibular gingiva on the left side**

**Coronal T2W MR image with fat suppression where a neoplastic change of the mandibular gingiva on the left side can be seen (pathohistological confirmation) spreading to the floor of the mouth and the equilateral neck region (arrow).

Figure 3. Squamous cell carcinoma of the mandibular gingiva on the left side[2]***

***Axial T1W MR image showing a peripheral postcontrast tumorous mass signal intensity increase with areas of central necrosis, surrounding tissue infiltration and spreading to the retromolar triangle (arrow).

Squamous cell carcinoma of the buccal region and gums

Even though only 10% of all oral cancers are localized in these regions they represent a potential danger for the surrounding bone structures and their invasion. Buccal tumors are most frequently arising from the lateral margin of the mouth and spread through submucosa, alongside buccinator muscle towards pterygomandibular raphe and bone cortex, affecting masticatory space, the skin, tonsils and soft palate. Regional metastases occur early affecting the submandibular, facial, parotid and periauricular lymph nodes. SCC of the gums arises from the edge of premolars and molars, where the most common radiological sign is the bone destruction with metastases present in level I and II lymph nodes.

Squamous cell carcinoma of the hard palate

Tumors of this region can occur in the middle or lateral parts of hard palate. It is of great importance to estimate the degree of bone invasion and to exclude perineural spreading, which could also be seen in adenoid cystic carcinoma and lymphoma. The tumor can spread along the greater and lesser palatine nerve into the pterygopalatine fossa, from where along the maxillary nerve through the foramen rotundum, progresses through infraorbital foramen or along the Vidian's nerve in the Vidian channel. In the advanced stage of the disease the invasion of the upper jaw, nasal cavity, buccal mucosa, tongue or retromolar triangle can occur. Lymphogenic dissemination affects facial, retropharyngeal lymph nodes and level II lymph nodes.

Atypical forms of squamous cell carcinoma

Atypical forms of SCC are the variants with special histological and immunohistochemical characteristics, such as verrucous carcinoma or basaloid squamous cell carcinoma (6,12,14).

Verrucous carcinoma or Ackerman's tumor typically occur on the buccal mucosa or lower jaw gums in older males that consume tobacco. Clinical appearance of these tumors is in a form of papilla, where in the early stage it has an excellent prognosis after the surgical treatment. Locally invasive forms can affect the mandible, while the metastases in the regional lymph nodes almost never occur.

Basaloid squamous cell carcinoma occurs in males in their sixth or seventh decades with the history of pronounced tobacco and alcohol consumption. It represents a exophytic ulcerative formation, most frequently in the region of the floor of the mouth and has a bad prognosis. The diagnosis of these tumors is a late one and the tumors aggressive behavior is reflected in perineural invasion, regional and distant metastases in the lungs, liver, bones, brain and skin. Compared to other types of the same region carcinomas, basaloid squamous cell carcinoma shows a high percentage of recidives, distant metastases and shorter survival rates.

Other malignant tumors of the oral cavity

The tumors with the highest incidence in this group are small salivary gland tumors and lymphomas.

Small salivary gland carcinomas are the second most common tumors of the oral cavity. It is considered that there is around 500-1000 small salivary glands in the mouth and oropharynx, especially in the region of soft and hard palate where, on their junction, these tumors occur most frequently. Opposite to SCC, these carcinomas occur in younger persons, in their fifth and sixth decade, with an equal distribution between the genders. They are characterized with a slow growth rate and most commonly with local invasion and better prognosis. Histologically two forms can be distinguished: adenoid cystic carcinoma, which is the most common mucoepidermoid carcinoma. There are three types of adenoid cystic carcinoma: cribriform (grade I), tubular (grade II) and solid (grade III). Depending on the grade of malignancy, characteristic submucosal and perineural spreading, along the maxillary or mandibular nerve, can be encountered. CT examination reveals a homogenous postcontrast density increase, with possible signs of hard palate bone erosion and an expansion of the grater palatine and round opening. Using MRI, low signal intensity in T2W points to the high grade tumors with high cellularity, while high signal intensity using the same sequence corresponds to low grade types and have a better prognosis. On the postcontrast T1W image the increase in tumor and maxillary nerve intensity can be observed. Regional lymph node metastases are rare, which is the opposite to mucoepidermoid carcinomas where metastases are frequent.

Although Hodgkin and non-Hodgkin lymphomas are common in the head and neck region, primary lymphomas of the oral cavity and oropharynx are rare and they most commonly affect the structures of Waldeyer's ring. In the oral cavity the nodal form of non-Hodgkin lymphoma in the submandibular space can occur. It is represented with multiple, enlarged and mostly non-necrotic lymph nodes, on both sides at the level I. They are revealed by the homogenous postcontrast signal intensity increase, except in the case of the high grade form with central necrosis (12, 14).

Conclusion

Although the presence of oral cavity carcinomas, due to their localization, can be detected in early stages by inspection, most of the diagnosed cases are in advanced stages of the disease. Due to the mentioned issues the involvement of contemporary radiological examination, such as computerized tomography and magnetic resonance imaging, during the diagnosis is of vast importance. Their use is necessary for disease staging, which influences further therapeutical treatment.

Reliability and precision of these imaging methods depends on the adequate radiological criteria application, especially TNM staging system, optimal scanning techniques, with the necessary knowledge of the radiological anatomy and pathology of this region.

The application of positron emission tomography, together with the imaging techniques, would allow more precise diagnosis and a greater chance for improvement in the patient's state.

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RADIOLOŠKA DIJAGNOSTIKA MALIGNIH TUMORA USNE DUPLJE

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Usna duplja, zajedno sa usnim delom ždrela, predstavlja najviši deo digestivnog trakta, jedinstven po složenoj anatomiji i tkivnoj strukturi unutar malog prostora. Posmatrajući oblast glave i vrata, oralne karcinome odlikuju visoka učestalost i mortalitet, multifaktorijalna etiologija i najčešće kasno postavljena dijagnoza. Njihova prognoza, kao i kod većine tumora, zavisi od stadijuma bolesti. Preko 90% svih malignih tumora usta i orofarinksa histopatološki pripada skvamocelularnom karcinomu. Njihova klinička procena se zasniva na inspekciji i palpaciji, uz neurološku procenu stanja kranijalnih nerava. Upotreba kompjuterizovane tomografije (CT) i magnetne rezonancije (MR) ključna je u definisanju raširenosti karcinoma usne duplje i planiranju adekvatnog terapijskog postupka. Poznavanje radiološke anatomije i patologije ove regije od presudne je važnosti u donošenju adekvatnog zaključka.
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Ključne reči: *maligni tumori usne duplje, skvamocelularni karcinom, CT, MR*