

# Histopathological Analysis of Metastatic Tumours of the Oral Cavity with Example of Metastatic Renal Cell Carcinoma to Tongue

## SUMMARY

**Background/Aim:** Metastatic tumours make up only 1-3% of all malignant tumours of the oral region; however, in 25% of the total number of cases, they are the first sign of the disease. Usually, metastases in the oral region are followed by poor prognosis. Metastases are more common in the mandible than in the maxilla; in soft tissues, they most commonly occur in the attached gingiva and tongue. Malignant tumours of the lung, breast, kidney, liver, bone, prostate, thyroid gland, skin, colon and female genital organs most commonly give metastases in this region, usually in patients aged 40 to 70 years. **Case Report:** We present a patient aged 79 years with a tumour change in the body of the tongue. After histopathological and immunohistochemical analysis (Cytokeratin, Vimentin, CD 10 positive tumour cells, Cytokeratin 7, Cytokeratin 20 negative tumour cells), there was a suspicion of metastasis of clear cell renal carcinoma (CCRC). Due to renal cancer, the patient had left kidney operated seven years before the diagnosis of tongue tumour. **Conclusions:** Diagnosis of metastatic tumours of the oral region is a great challenge, both for clinicians and for histopathologists. Since it is a heterogeneous group of neoplasms, standard histopathological tissue processing, is not always sufficient to determine the histological type of tumour and its primary origin. In the analysis of metastatic tumours of the oral region, team work is important and careful clinical and histopathological assessment lead to definitive and accurate diagnosis.

**Key words:** Metastasis, Oral Cavity, Immunohistochemistry, Renal Carcinoma

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## CASE REPORT (CR)

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## Introduction

Metastatic tumours make up only 1-3% of all malignant tumours of the oral region; however, in 25% of the total number of cases, they are the first sign of the disease. Usually, metastases in the oral region are followed by poor prognosis. Metastases can occur in soft tissues of the oral region, although they are more common in bone structures. Metastases are more common in the mandible than in the maxilla; in soft tissues, they most commonly occur in the attached gingiva and tongue. The pathogenesis of metastases to jaw bones and gingiva is not completely understood. Remnants of active bone marrow may serve as a favourable location for metastatic tumours' cells.

Chronic inflammation of gingiva may provide adequate conditions for metastatic tumour cell colonisation<sup>1-3</sup>.

These tumours most commonly occur in patients aged 40 to 70 years. Malignant tumours of the lung, breast, kidney, liver, bone, prostate, thyroid gland, skin, colon and female genital organs most commonly give metastases in oral region. The incidence of metastatic tumours of oral region is rising, according to the fact that patients with cancers live longer due to advances in cancer diagnosis and management<sup>2,4-6</sup>.

The diagnosis of metastatic tumours is great challenge for both, clinicians and pathologists. It is important that clinicians should recognize the possibility of a metastatic tumour and pathologists should determine

the site of origin. Dentists have a key role in the diagnosis of metastatic tumours of the oral region, especially in cases where metastatic disease is the first sign of an undiagnosed tumour in the other part of the body<sup>1-3</sup>.

Since metastatic tumours of oral region are a heterogeneous group of neoplasms, standard histopathological tissue processing is not always sufficient to determine the histological type of tumour and its primary origin. Therefore, sometimes is necessary to perform an immunohistochemical analysis of tumour tissue<sup>3,7-9</sup>.

For the purpose of quality histopathological analysis, it is necessary to provide an adequate sample of tumour tissue. After routine haematoxylin eosin staining and analysis of tumour tissue morphology, the next step is immunohistochemical analysis in order to determine histological type of tumour and the site of origin. An important fact is the previous history of malignant disease, so that the pathologist can do a morphological comparison of the primary and metastatic tumours. The most common metastatic deposits are given by carcinomas, mainly adenocarcinomas<sup>1,3,6,8</sup>.

On the third place in the frequency of metastasis in the region of the head and neck (after lung and breast cancer) is the renal carcinoma, especially clear cell renal carcinoma (CCRC). This type of tumour most often gives metastases to the nose and paranasal sinuses, then in the oral region. When the oral region is concerned, metastases in the gingiva and in the tongue are most frequently observed. Oral metastases of renal carcinoma are the most common manifestation of an extended disease, followed by a poor prognosis<sup>10-12</sup>.

The aim of this report is to present the patient with the CCRC metastasis in the body of the tongue.

## Case Report

A male, aged 79, was referred because of tumour in the body of the tongue. The tumour was clearly limited in relation to the surrounding tissues of the tongue, while the mucosa above the tumour was preserved. After preoperative preparation, tumour extirpation of the oval tissue fragment, sized 39x31x12 mm with smooth surface, was performed. On the serial cuts the fragment was yellow coloured with soft consistency.

A microscopic examination showed connective tissue, salivary gland and skeletal muscle cells at periphery, while the bulk of the delivered fragment was a tumour tissue built from solid and alveolar arrangements of medium-sized, round and polygonal atypical cells, with bright cytoplasm, small and pleomorphic nucleus and prominent nucleolus. The tumour stroma was scarce with many blood vessels of the capillary type. The tumour was clearly limited in relation to surrounding connective tissue

(Figure 1). In the blood vessels of the connective tissue there were groups of tumour cells. The results of immunohistochemical analysis of tumour cells were: positive for AE1/AE3 (Figure 2), positive for Vimentin (Figure 3), positive for CD 10 - canalicular positivity (Figure 4), while CK7, CK20 and S100 were negative.

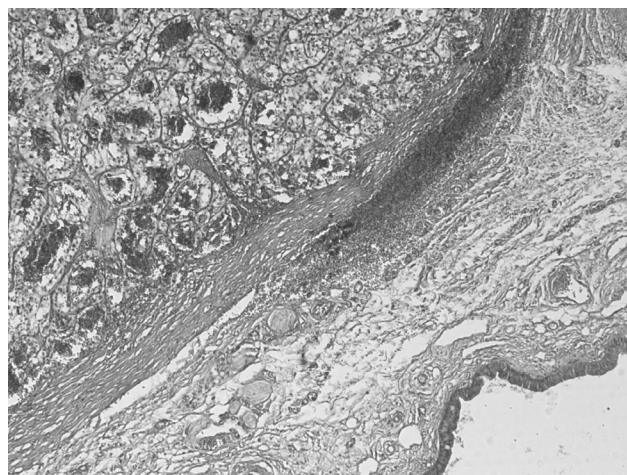


Figure 1. Tumour tissue and salivary gland duct of tongue, haematoxylin - eosin, 5x

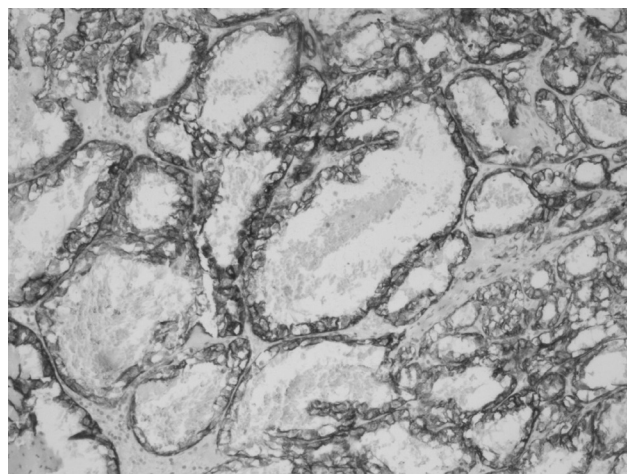


Figure 2. Tumour tissue, cytokeratin, 10x

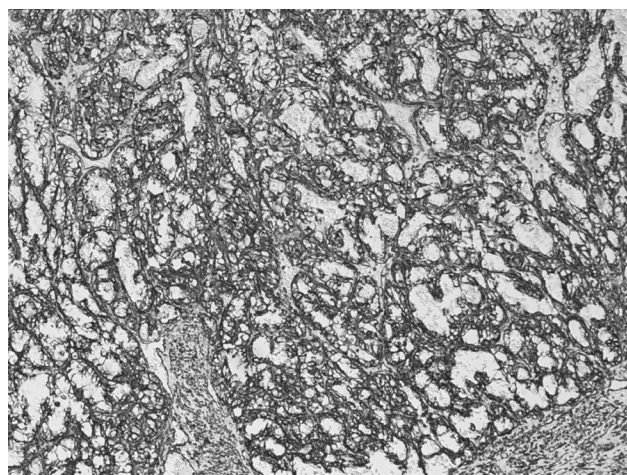


Figure 3. Tumour tissue, vimentin, 5x

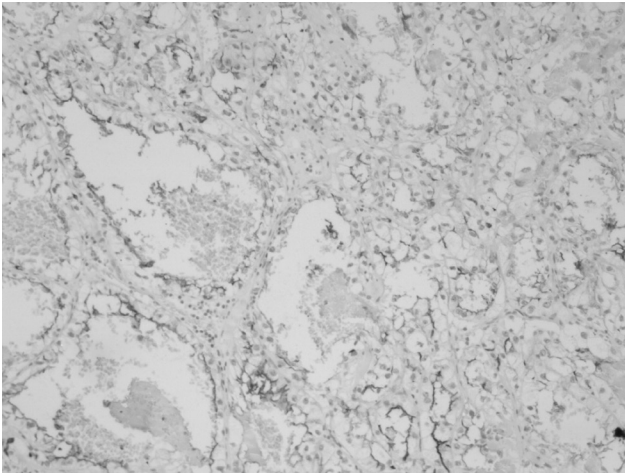


Figure 4. Tumour tissue, CD10, 10x

Based on the method of growth of tumour cells, morphology and immune-histochemical analysis, the pathohistological diagnosis was a malignant tumour of the tongue with clear cell morphology, resembling the CCRC metastasis in the tongue.

The patient was presented with a histological report to the oncology consulting body in order to make a definitive conclusion. By inspecting the complete medical documentation, and considering the fact that the patient had nephrectomy with a pathohistologically verified CCRC (T1b stadium of the disease), seven years before diagnosis of tongue tumour, clinical data supported the pathohistological diagnosis towards the metastatic deposit of CCRC in the tongue. After consultative examination of the patient, computerized tomography (CT) of the chest and abdomen was requested. On the chest CT examination, there were mutually identified nodes susceptible to secondary deposits, in the right lung largest was 12 mm, and in the left lung 13 mm. Pleural space was clear. Lymph nodes of up to 24 mm diameter were noticed in the mediastinum. At the abdominal CT, there were no signs of recurrence in the lodge of the operated kidney, as well as secondary deposits in the abdomen organs and bone structures. The patient was referred to an oncology consulting body for further treatment decisions.

## Discussion

Metastatic tumours to the oral cavity are a rare event. Only 33% are seated in the soft tissues. Metastatic tumours to gingiva are very often polypoid or exophytic, well vascularized masses. In tongue, metastatic tumours most commonly appear as submucosal masses. These tumours are complications of systemic cancer and usually develop in the late stage of the disease<sup>1</sup>.

In cases of poorly differentiated malignant tumours, an immunohistochemical analysis is necessary in order to determine the histogenetic origin of the tumour cells. It is necessary to use the following panel of immunohistochemical markers: pancytokeratin and p63 (to confirm carcinoma), vimentin (to confirm sarcoma), S100 (to confirm melanoma) and LCA (to confirm lymphoma). Most metastatic tumours in the oral region are carcinomas (in 90% of cases). In some cases, such as well-differentiated carcinomas of the liver, thyroid glands and kidney, it is possible to suspect, on the basis of morphology, the primary origin of the tumour<sup>8,13</sup>. Most commonly, after a basic immunohistochemical marker panel, and confirmation that it is a cancer, it is necessary to use: cytokeratin 7 (CK7) and cytokeratin 20 (CK20) antibodies in order of further subclassification of the tumour. A tumour tissue profile that implies CK7 negative (-) and a CK20 positive (+) tumour probably suggests a colorectal cancer or Merkel skin cancer. Tumours showing the CK7 + / CK20 - profile are most likely of primary origin in the lungs, breast, thyroid gland, endometrium, cervix, pancreas, or biliary ducts. Profile CK7 + / CK20 + is the most common characteristic of urothelial cancers, ovarian cancer, pancreatic cancer and cancers of biliary ducts. Hepatocellular liver carcinoma, renal carcinoma, prostate and squamous carcinoma usually have profile CK7- / CK20-. Stomach cancer has a variable profile - in certain percentages all CK7 and CK20 combinations may exist<sup>2,8,9,13</sup>.

The next line of immunohistochemical markers implies the use of tissue-specific markers. For example, prostate cancer (CK7- / CK20-) is positive for Prostate specific antigen (PSA), Prostate Acid Phosphatase (PSAP), Prostate Specific Membrane Antigen (PSMA), P501S (prostein) and NKX3.1. The colorectal carcinoma is positive for the carcinoma-embryonic antigen and CDX2. Carcinoma of bile ducts is positive for cytokeratin 19. The urothelial carcinoma is positive for Urothelin and WT1, while hepatocellular liver carcinoma is positive for Hep Par 1<sup>3,4,6,8,13</sup>.

Particularly speaking about clear cell morphology tumours in the oral region, primary tumours are very rare, more often they are metastases of the CCRC<sup>14,15</sup>. In the differential diagnosis of the clear cell morphology oral tumours, benign lesions, primary malignant tumours and metastatic tumours should be considered<sup>16</sup>. Among benign lesions, in differential diagnosis, it is important to consider a pyogenic granuloma. Yoshitomi et al<sup>11</sup>, showed a case where the RCC metastasis in the tongue was replaced clinically with a pyogenic granuloma. In the differential diagnosis of malignant tumours with clear cell morphology, clear cell tumours of the salivary glands, primary and metastatic melanoma and metastatic clear cell carcinoma (usually CCRC) should come under consideration. Similar to primary tumours, metastatic

tumours may look polypoid or ulcerative, so clinical and pathohistological differential diagnosis could be difficult<sup>16</sup>.

Immunohistochemical staining in addition to morphology is necessary in establishing the diagnosis of metastatic renal carcinoma. Metastatic CCRC, unlike salivary carcinoma, shows positivity to pancytokeratin, vimentin and CD10<sup>12</sup>. Salivary gland myoepithelial carcinoma of clear cell morphology is a rare tumour, first shown in the literature in 2011 by Park and others<sup>17</sup>, is positive for epithelial markers (EMA, CK), as well as at least two myoepithelial markers (S100, calponin, p63 or actin).

Renal carcinoma, particularly CCRC is characterized by an unpredictable clinical course. Metastases may occur years after diagnosing the primary tumour. The prognosis of patients with lingual metastases of the CCRC is poor, the average survival interval is considered to be 5.8 months<sup>12,18</sup>. In the presented case, the CCRC gave the oral metastasis 7 years after nephrectomy, based on the morphology of tumour tissue, as well as the immunohistochemical profile of tumour cells.

## Conclusions

In the analysis of metastatic tumours of the oral region, team work is important and careful clinical and histopathological assessment lead to definitive and accurate diagnosis. Unfortunately, there are cases (especially in cases of poor and undifferentiated carcinomas) in which even after immunohistochemical analysis, it is not possible to define the histological type and primary tumour origin.

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