

Case report

## Cervical Lymph Node Metastases from Unknown Primary Tumor

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### Abstract

**Introduction:** Metastases of the lymph nodes of the neck originating from cancers of an unknown primary site represent a diagnostic and therapeutic challenge. Metastatic carcinomas of unknown primary site (CUPS) account for about 3-5% of all malignant disease diagnoses. Planocellular carcinomas account for 90% of cancers of unknown site, while the remaining 10% are poorly differentiated and adenocarcinomas.

**Materials and methods:** This paper presents three case reports of patients with surgical treatment at the Department of Maxillofacial Surgery, Clinical Hospital, Stip, who had metastases of the lymph nodes of the neck with the unknown primary tumor site.

**Results:** We follow diagnostic protocols which include a detailed clinical examination, radiological diagnostics, fine needle biopsy (FNAB) of the tumor change in the neck, esophagogastroduodenoscopy, detailed examination of the naso, oro and hypo pharynx, evaluation of the laryngeal structures. In all patients, after the clinical evaluation, ultrasonography, otorhinolaryngological examination, neck CT and fine needle biopsy were performed. FNAB findings showed metastatic deposits from squamous cell carcinomas. The therapy of metastases from CUPS includes surgical treatment (neck dissection) and the use of radiotherapy (RT), and some authors also recommend chemoradiotherapy, in cases with advanced regional disease.

**Conclusion:** Significant advances in diagnostic and operative techniques have increased the probability of identifying the primary tumor, as well as its regional and systemic spread. If CT or MRI does not identify a primary site, PET/CT scans should be performed before surgical biopsy. Although high-quality data on treatment protocols are lacking, patients with more advanced stages of regional disease require combined treatment that includes neck dissection, and postoperative radiotherapy with or without chemotherapy.

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## Introduction

Carcinoma of unknown primary site (CUPS) is a heterogeneous group of cancers defined by the presence of metastatic disease with no identified primary tumor at presentation.

One of the first symptoms of the existence of a malignant process whose localization has not been identified is a painless swelling in the neck area due to metastatic changes in the lymph nodes. Very few oncological diseases pose such difficult diagnostic and therapeutic dilemmas for surgeons as metastatic tumors with unknown primary site (Cancer Unknown Primary Site – CUPS).

The purpose of imaging for lymph node (LN) metastasis from an unknown primary site is to identify the primary tumor or detect its absence, which leads to the correct diagnosis and optimal treatment. The authors discuss diagnostic imaging approaches for identifying the primary tumor in cases of unknown primary cervical LN metastases. The distribution and characteristics of LN metastases may help locate the primary site. Unknown primary LN metastasis often occurs at nodal levels II and III, and in recent reports, these were mostly related to human papillomavirus (HPV)-positive squamous cell carcinoma of the oropharynx. Another characteristic imaging finding suggestive of metastasis from HPV-associated oropharyngeal cancer is a cystic change in LN metastases. Other characteristic imaging findings such as calcification may help predict the histologic type and locate the primary site. In cases of LN metastases at nodal levels IV and VB, a primary lesion located outside the head and neck region must also be considered. One clue for detecting the primary lesion at imaging is the disruption of anatomic structures, which can help in identifying small mucosal lesions or submucosal tumors at each subsite. Additionally, fluorine 18 fluorodeoxyglucose PET/CT may help identify a primary tumor. These imaging approaches for identifying primary tumors enable prompt identification of the primary site and assist clinicians in making the correct diagnosis.

The definition of metastatic tumor of unknown primary site - Cancer of unknown primary site (CUPS) implies a histologically proven metastatic malignant epithelial disease, without an identified primary localization, despite detailed investigations, which include: a detailed clinical examination of the head, face, ears and oral cavity, furthermore, fiberoptic examination of the oral cavity, pharynx, larynx, and sinonasal cavity, including areas not visible at clinical inspection, should also be performed, gynecological and rectal examination, complete biochemical analyses, CT of the head, chest and abdomen, immunohistochemical analysis of the histological material. Fine-needle aspiration of a neck mass is necessary to establish the histologic diagnosis. It is recommended to use p16 testing for cervical LNs with carcinoma of an unknown primary site, especially for LN metastasis at nodal levels II or III, while EBV testing is used for p16-negative metastases, which indicate nasopharyngeal cancer (1).

The exact incidence is difficult to estimate because these patients are often treated under other diagnoses and thus are not adequately represented in tumor registries. Various authors report an incidence of these diseases of about 3-5% of all malignant diseases of the head and neck (2). The average age limit of the patients is about 60 years, with a somewhat more frequent occurrence in men (3).

The most common primary sites for SCC cervical LN metastasis from an unknown primary tumor are reported to be the oropharynx (palatine tonsil, 45%; base of the tongue, 44%), hypopharynx, and nasopharynx (4). The frequency of unknown primary SCC has recently shown an increasing trend, and 60%-90% of unknown primary SCCs are p16 positive, which is strongly suggestive of a primary site in the palatine or lingual tonsils (5). For histologic types other than SCC, the possible primary sites in the head and neck region are the thyroid gland and salivary glands. Primary sites outside the head and neck region may include the lung, breast, uterine cervix, and stomach (6).

The predominant histological type is squamous cell carcinoma, with representation in 75-90% of

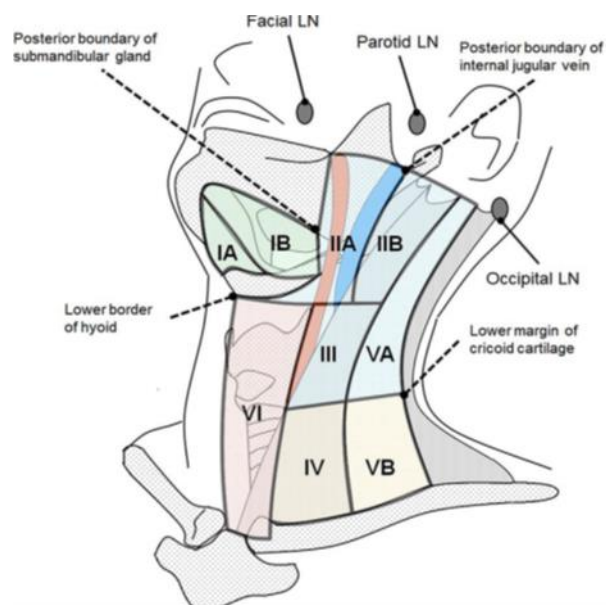
cases, while a smaller percentage is represented by undifferentiated carcinomas and adenocarcinomas (7). Identification of the primary location of the tumor allows better planning of surgical treatment, which is associated with a better prognosis and survival time. In the last decade, several national guidelines have been presented recommending strategies for diagnosis and treatment (8,9), but a consensus on the diagnostic approach of head and neck CUPS has not yet been reached.

CUPS is characterized by a silent primary focus, a high degree of aggressiveness and early metastasis in regional lymph nodes. The primary tumor has a slow growth, unlike the secondary deposits, that is, it becomes involuted, and therefore more difficult for early detection. Clinically, it presents with symptoms caused by the metastases, as well as general symptoms, such as anorexia, weight loss, and fatigue.

Treatment of head and neck CUP prioritizes loco-regional control. Initial recommendations include surgical treatment (neck dissection) with radiotherapy (RT) (10,11). Chemotherapy is recommended for emphasized N2,N3 and metastases with extracapsular extension (12,13).

However, the treatment of these diseases remains heterogeneous and is based on clinical experience and institutional policies.

The distribution of cervical LN metastases can be broadly divided into the following three areas, which are useful for predicting the primary site: (a) nodal levels II, III, and VA; (b) nodal levels IV and VB; and (c) other LNs, including level I, parotid LNs, and superficial lateral, facial, and occipital LNs (Fig 1, Table 1) (14).



**Figure 1. Anatomic boundaries of the neck levels and sublevels according to the American Head and Neck Society classification system. Adapted from Robbins et al. (14).**

**Table 1. Primary Site Predicted from Distribution of Cervical LN Metastases**

Distribution of LN Metastases	Potential Primary Site
Levels II, III, VA	Oropharynx( palatine tonsil and the base of tongue ), nasopharynx and hypopharynx
Levels IV, VB , VI	Hypoprahynx , supraglottic, cervical esophagus , thyroid gland, thorax, abdomen (lung, breast, esophagus, gastric, gynecologic ,etc)
Other LNs	
Parotid and superficial lateral LNs	Parotid gland, cutaneous face, scalp, sinonasal cavity
Levels IA , IB	Floor of mouth, submandibular gland, anterior oral cavity , sinonasal cavity, lips , periorbital issues, cutaneous face
Facial LNs	Cutaneous face, oral cavity
Occipital LNs	Scalp, cutaneous face

The prognosis of this disease is poor, and survival is 4-13 months, despite treatment. The extreme variety in the manifestation, the metastatic character of the disease at the time of diagnosis and the poor response to therapy have resulted in little interest of researchers in this problem. This is the main reason why we were motivated to investigate this problem and to present case reports from our clinical practice.

## Materials and Methods

### *Case reports from our clinical practice*

The presented case reports were diagnosed and treated at the Department of Maxillofacial Surgery, Clinical Hospital, Stip, North Macedonia. In order to present the data in this paper, we followed the ethical rules, and each respondent and his companion signed an informed consent.

### *Case Report 1*

A 72-year-old patient came to the Department of Maxillofacial Surgery, Clinical Hospital, Stip, because of a painless swelling in the left parotid region. Anamnestic data for its existence is about 4 months. On examination the patient did not report any other relevant head and neck symptoms or any comorbidities. He was a smoker, up to 60 cigarettes per day, for the last 10 years with reduced intensity. Clinically, on inspection, a tumor mass is evident, painless, fixed to the substrate, the size of an orange, without changes in the covering skin. After the ultrasonography, a tumor formation was found, with a heterogeneous structure, with a diameter of about 4 cm. A careful otorhinolaryngological examination was performed, with flexible nasopharyngo-laryngoscopy. The clinical ORL finding was normal. Before admission and surgical treatment, head, neck and chest CT was performed with intravenous contrast. CT findings indicated metastatic disease in the right parotid region, with central necrosis and infiltration of surrounding structures. A histopathological diagnosis of metastatic squamous cell carcinoma (SCC) was obtained by fine needle biopsy (FNAB). Intraoperative findings showed infiltration of the superficial

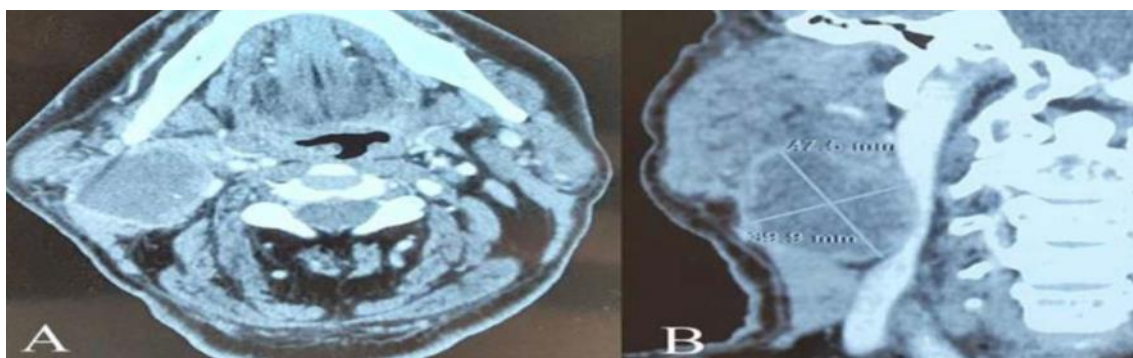
lobe of the parotid gland, and the posterior bellows of the digastric muscle. A complete removal of the metastatic deposit was performed unblock with the superficial lobe of the right parotid gland and the posterior bellows of the digastric muscle. The pathohistological finding was consistent with metastatic SCC, confirming parotid lymph node metastases. With the decision of the oncology board, the patient underwent postoperative RT of the neck (from the skull base to the cricoid cartilage), including ipsilateral neck level II, III, IV and parotid gland. Regular controls were made at the Department of Maxillofacial Surgery, Clinical Hospital, Stip, in the first two years after the operation, every six months. After two years of regular oncological controls, the patient was lost to follow-up.



**Figure 2. Preoperative status**



**Figure 3. Intraoperative finding**



**Figure 4. and 5. CT finding of the neck with intravenous contrast**

Two years after the operation, the patient developed difficulties in swallowing. On additional otorinolaryngological examination, with indirect laryngoscopy, a pharyngeal tumor was found on the left lateral oro-hypopharyngeal wall, with extension to the piriform fossa and involvement of the right larynx. Biopsy with histopathological examination confirmed the diagnosis of SCC. CT scan of the head, neck and chest showed no signs of regional or distant disease spread. The patient underwent total pharyngolaryngectomy, tracheostomy and left selective neck dissection. The patient received postoperative RT (60 Gy in 30 fractions). Five months after RT, the patient was free of recurrent disease.

#### Case Report 2

A 77-year-old patient was referred to the Department of Maxillofacial Surgery, Clinical Hospital, Stip, due to the presence of an infiltrative-ulcerative change in the right parotid region, which also extends retroauricularly. According to information from a family member, the change appeared about eight months ago as a subcutaneous spherical formation, with gradual growth. Due to no adherence to the therapeutic process, patient refused to stay in the hospital. As result of this, during the long period of time, there is a rapid growth of the change and the appearance of ulceration in the parotid region. Echotomography on the right side of the neck revealed a large infiltrative, ulcerated lesion, with central necrosis, and pathologically enlarged lymph nodes on the

neck. An incisional biopsy of the change was made, which pathohistologically showed that it was a metastatic deposit from carcinoma of epithelial origin. Considering the comorbidities present (two previous strokes, decompensated cardiac condition) after the preoperative anesthesiological assessment, the patient was refused surgical treatment and was referred to Oncology for further treatment.

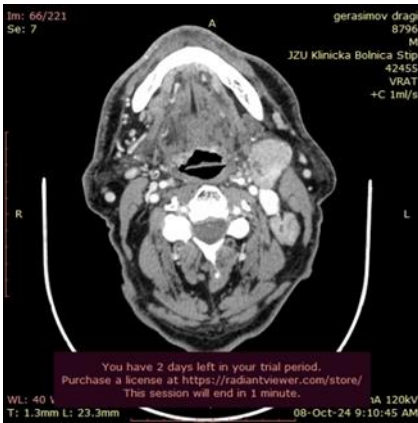


**Figure 6. Clinical picture**

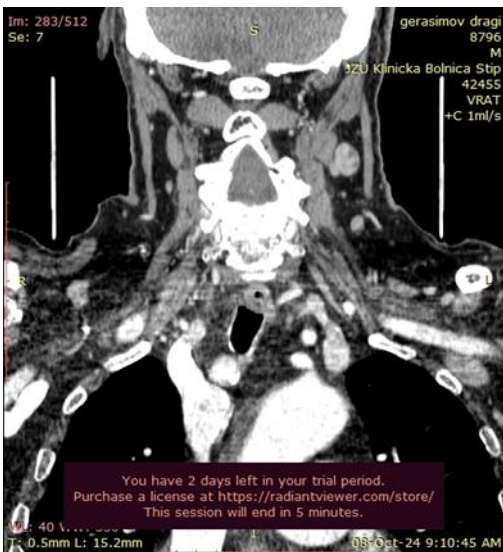
#### Case report 3

A 72-year-old patient came for an examination at the Department of Maxillofacial Surgery, Clinical Hospital, Stip due to swelling on the left side of the neck. The swelling is painless, with a hard consistency, fixed. An ultrasonographic examination and a fine needle biopsy were

performed. The result of the histological examinations is a metastatic deposit of cancer of epithelial origin. A CT scan of the head, neck and lungs was performed. The finding of the lung parenchyma is without focal diseases.



**Figure 7. CT finding of the neck with contrast - preoperative**



**Figure 8. CT finding of the neck with contrast - preoperative**

An otorinolaryngology examination was also performed, with a nasoropharyngolaryngeal evaluation, during which no pathological changes were detected. The findings of the esophago-gastro-duodenoscopy were normal. An indication for surgical treatment has been established. The operation was performed in endotracheal anesthesia. A complete removal of the metastatic deposit was performed. The postoperative course was uneventful. The patient was released for home treatment 5 days

after the operation. An immunohistochemical analysis was performed on the preparation, which showed involvement of lymph nodes on the neck with a metastatic deposit of moderately differentiated invasive squamous cell carcinoma, which penetrates the capsule with the presence of emboli from malignant cells in the lymphocytes around the capsule of the lymph node.

Immunohistochemical profile:

1. CK 5/6 – negative
2. CK MNF 116 +++ positive
3. p63 ++++ strongly positive



**Figure 9. Prepare for histopathological examination**



**Figure 10. Intraoperative finding**

Two weeks after the operation, the patient is referred to Oncology, where radiotherapy is prescribed.

## Results and Discussion

The inability to detect the location of the primary tumor in a patient with metastatic CUPS represents a clinical challenge that can affect the course of treatment and the prognosis of the disease. After clinical examination and diagnostic imaging (ultrasonography, CT), aspiration biopsy (FNAB) is crucial in the assessment of neck tumor mass in CUPS. The American Joint Committee on Cancer (AJCC) recommends adding HPV assessment (staining) to diagnostic procedures (15).

With positive immunohistochemical staining of the specific HPV marker - p16, it would indicate a potential oropharyngeal primary tumor (palatine tonsils and base of tongue). Lymph node metastases with CUPS were positive for HVP in 7.8% to 30% of patients (16).

PET/CT is recommended in those patients in whom conventional imaging has failed to identify the primary tumor site, PET/CT has a high sensitivity (up to 88.3%) making it an excellent additional diagnostic procedure (17,18). Diagnostic protocols using preoperative PET/CT, which would precede EGD (esophago-gastro-duodenoscopy) with directed biopsies, have resulted in detection of the primary lesion in over 90% of patients (19-21). The National Comprehensive Cancer Network (NCCN) provides recommendations for endoscopic examination (nasopharyngoscopy), inspection and palpation of the oral cavity and oropharynx, laryngoscopy, bronchoscopy. Oropharyngeal locations, particularly the tonsils and base of the tongue, are the most common sites for primary occult tumors.

Treatment of patients with unknown primary cancer with neck metastases includes neck dissection, followed by postoperative RT or consideration of chemo-RT 14. According to some reports, patients undergoing bilateral RT did not have a significant increase in survival and

regional recurrences, compared to patients treated with unilateral RT of the neck and mucosal surfaces. On the other hand, some studies favor bilateral nodal and mucosal irradiation (22).

The NCCN recommends combined chemo-RT in cases of N2/N3 neck lymph nodes present with extracapsular extension (23,24), although it is noteworthy that no randomized trials have demonstrated the superiority of this treatment over RT alone. Due to the low incidence of the disease and the lack of high-quality data, there are still no clear clinical protocols for these diseases.

## Conclusion

A focused search for the primary tumor is recommended in CUP cases. Identifying patients with prognostically favorable disease is important, since they may have substantial benefit from directed treatment and experience prolonged survival.

Significant advances in diagnostic and operative techniques and the application of digital technology have increased the probability of identifying the primary tumor, as well as its regional and systemic spread. If CT or MRI does not identify a primary site, PET/CT scans should be performed before surgical endoscopy and biopsy. Although high-quality evidence-based treatment protocol data are lacking, patients with more advanced stages of regional disease require combined treatment that includes neck dissection and postoperative radiotherapy with or without chemotherapy.

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## Disclosure

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**Competing interests.** None to declare.

## References

1. Maghami E, Ismaila N, Alvarez A, et al. Diagnosis and Management of Squamous Cell Carcinoma of Unknown Primary in the Head and Neck: ASCO Guideline. *J Clin Oncol* 2020;38(22):2570–2596.
2. Kalavacherla S, Sanghvi P, Lin GY, Guo T: Updates in the management of unknown primary of the head and neck. *Front Oncol*. 2022, 12:991838. 10.3389/fonc.2022.991838
3. Altman E, Cadman E. An analysis of 1539 patients with cancer of unknown primary site. *Cancer* 1986, 57; 120-124.
4. Cianchetti M, Mancuso AA, Amdur RJ, et al. Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site. *Laryngoscope* 2009;119(12):2348–2354
5. Cummings MA, Ma SJ, Van Der Sloot P, Milano MT, Singh DP, Singh AK. Squamous cell carcinoma of the head and neck with unknown primary: trends and outcomes from a hospital-based registry. *Ann Transl Med* 2021;9(4):284.
6. Kennel T, Garrel R, Costes V, Boisselier P, Crampette L, Favier V. Head and neck carcinoma of unknown primary. *Eur Ann Otorhinolaryngol Head Neck Dis* 2019;136(3):185–192.
7. Shah JP: Patterns of cervical lymph node metastasis from squamous carcinomas of the upper aerodigestive tract. *Am J Surg*. 1990, 160:405-9. 10.1016/s0002-9610(05)80554-9
8. Lydiatt WM, Patel SG, 'O'Sullivan B, Brandwein MS, Ridge JA, Migliacci JC, et al. Head and Neck cancers-major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin* 2017; 67: 122–37
9. Fizazi K, Greco FA, Pavlidis N, Daugaard G, Oien K, Pentherou-dakis G. ESMO Guidelines Committee. Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015; 26 Suppl 5: v133–8.
10. Pfister DG, Spencer S, Brizel DM, Burtness B, Busse PM, Caudell JJ, et al. Head and Neck Cancers, Version 1.2015. *J Natl Compr Canc Netw* 2015; 13(7): 847–55; quiz 856.
11. Mackenzie K, Watson M, Jankowska P, Bhide S, Simo R. Investigation and management of the unknown primary with metastatic neck disease: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol* 2016; 130(Suppl 2): S170–5.
12. Straetmans J, Vent J, Lacko M, Speel EJ, Huebbers C, Semrau R, et al. Management of neck metastases of unknown primary origin united in two European centers. *Eur Arch Otorhinolaryngol* 2015; 272(1): 195–205.
13. Milovanovic J, Andrejić D, Jotić A, Djukić V, Tošković O, Savić Vujović K, et al. The impact of socioeconomic factors on quality of life and functional impairment in patients treated for oropharyngeal carcinoma. *Vojnosanit Pregl* 2019; 76(6): 598–606.
14. Robbins KT, Shaha AR, Medina JE, et al. Consensus statement on the classification and terminology of neck dissection. *Arch Otolaryngol Head Neck Surg* 2008;134(5):536–538.
15. Fizazi K, Greco FA, Pavlidis N, Daugaard G, Oien K, Pentherou-dakis G. ESMO Guidelines Committee. Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015; 26 Suppl 5: v133–8.
16. Straetmans J, Vent J, Lacko M, Speel EJ, Huebbers C, Semrau R, et al. Management of neck metastases of unknown primary origin united in two European centers. *Eur Arch Otorhinolaryngol* 2015; 272(1): 195–205.
17. Klausner G, Troussier I, Blais E, Carsuzaa F, Zilli T, Miralbell R, et al. Neck management in head and neck squamous cell carcinomas: where do we stand? *Med Oncol* 2019; 36(5): 40.



18. Kuta V, Williams B, Rigby M, Hart R, Trites J, MacKay C, et al. Management of head and neck primary unknown squamous cell carcinoma using combined positron emission tomography-computed tomography and transoral laser microsurgery. *Laryngoscope* 2018; 128(10): 2307-11.
19. Klausner G, Troussier I, Blais E, Carsuzaa F, Zilli T, Miralbell R, et al. Neck management in head and neck squamous cell carcinomas: where do we stand? *Med Oncol* 2019; 36(5): 40.
20. Kuta V, Williams B, Rigby M, Hart R, Trites J, MacKay C, et al. Management of head and neck primary unknown squamous cell carcinoma using combined positron emission tomography-computed tomography and transoral laser microsurgery. *Laryngoscope* 2018; 128(10): 2307-11.
21. Waltonen JD, Ozer E, Schuller DE, Agrawal A. Tonsillectomy vs. deep tonsil biopsies in detecting occult tonsil tumors. *Laryngoscope* 2009; 119(1): 102-6
22. Arosio AD, Pignataro L, Gaini RM, Garavello W. Neck lymph node metastases from unknown primary. *Cancer Treat Rev* 2017; 53: 1-9.
23. Pflumio C, Troussier I, Sun XS, Salleron J, Petit C, Caubet M, et al. Unilateral or bilateral irradiation in cervical lymph node metastases of unknown primary? A retrospective cohort study. *Eur J Cancer* 2019; 111: 69-81.
24. Pfister DG, Spencer S, Adelstein D, Adkins D, Anzai Y, Brizel DM, et al. Head and Neck Cancers, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2020; 18(7): 873-98.

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**Author contribution.** Single author article

## Metastaze limfnih čvorova vrata od karcinoma nepoznatoga primarnog sijela

### Sažetak

**Uvod:** Metastaze limfnih čvorova vrata koje potječu od karcinoma nepoznatog primarnog sijela predstavljaju dijagnostički i terapijski izazov. Metastatski karcinomi nepoznatog primarnog sijela (CUPS) čine otprilike 3 – 5 % svih dijagnoza malignih bolesti. Planocelularni karcinomi čine 90 % karcinoma nepoznatoga sijela, dok preostalih 10 % otpada na slabo diferencirane i adenokarcinome.

**Materijali i metode:** Ovaj rad prikazuje tri prikaza slučajeva pacijenata kirurški liječenih na Odjelu za maksilofacijalnu kirurgiju, Klinička bolnica Štip, koji su imali metastaze limfnih čvorova vrata s nepoznatim primarnim sijelom tumora.

**Rezultati:** Pratili smo dijagnostičke protokole koji uključuju detaljan klinički pregled, radiološku dijagnostiku, citološku punkciju tankom iglom (FNAB) tumorske promjene na vratu, ezofagogastroduodenoskopiju, detaljan pregled nazo-, oro- i hipofarinksa te procjenu struktura larinksa. Kod svih pacijenata, nakon kliničke evaluacije, provedeni su ultrazvuk, otorinolaringološki pregled, CT vrata i FNAB. FNAB nalazi su pokazali metastatske naslage planocelularnih karcinoma. Terapija metastaza od CUPS-a uključuje kirurško liječenje (disekcija vrata) i primjenu radioterapije (RT), dok neki autori preporučuju i kemoradioterapiju kod slučajeva s uznapredovalom bolešću regije.

**Zaključak:** Značajan napredak u dijagnostičkim i operativnim tehnikama povećao je vjerojatnost identifikacije primarnog tumora, kao i njegovog regionalnog i sistemskog širenja. Ako CT ili MRI ne identificiraju primarno sijelo, potrebno je napraviti PET/CT pretrage prije kirurške biopsije. Iako nedostaju visokokvalitetni podaci o protokolima liječenja, pacijenti s uznapredovalim stadijima regionalne bolesti zahtijevaju kombinirano liječenje koje uključuje disekciju vrata te postoperativnu radioterapiju, s ili bez kemoterapije.