

*Medicinska edukacija*  
*/Medical education*

APPARITION, CLINICAL EVALUATION,  
DIAGNOSIS AND THERAPY OF  
METASTATIC LYMPH NODES IN THE NECK

PRISUSTVO, KLINIČKA PROCENA,  
DIJAGNOSTIKA I TERAPIJA  
METASTATSKIH LIMFNIH ČVOROVA  
U VRATU

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*Ključne reči*

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*Abstract*

Cervical lymph node metastases are the first symptom of malignancies in the head and neck region in a significant number of cases (12%-15%). Three factors leading to three different aetiologies of these adenopathies are: congenital, infectious and neoplastic. Adults should be suspected for a neoplastic origin at first. Initial diagnosis should be confirmed by cytological finding of the fine needle aspiration biopsy, which in most cases must be performed meticulously under ultrasound or X-ray guidance that rises diagnostic reliability over 85%. It is possible to establish correspondence between neck lymph node location and its lymphatic drainage system that leads to the most likely origin of the primary tumor. The cervical metastases from an unknown primary tumor account for more than 5% of all cases of metastatic neck disease. That's why the diagnosis needs random biopsies of the regions that are suspected to early dissemination. The location and histology, as well as a stage and detection of the primary tumor are the principal, main prognostic factors in the conditions mentioned above.

*INTRODUCTION*

It has been estimated that about 12%-15% of all head and neck tumors manifest in the form of cervical adenopathies (1). However, the detection of a neck lymphatic node metastasis requires the exclusion of a possible infectious process in the corresponding lymphatic drainage region, for example in cases where adenopathy is the first manifestation of the disease.

The assessment of a neck node secondary deposits should be made within the context of the differential diagnosis required for cervical tumefactions in general; therefore, maxillofacial surgeon must adopt the working protocol capable of yielding a prompt and reliable diagnosis.

The differential diagnosis of a neck tumefaction basically comprises three aetiologies: congenital, infectious and neoplastic. Seldom, in the specific case of a neck node mass, a congenital origin should be excluded, focusing attention to the two other possibilities.

*DIAGNOSIS*

*Anamnesis*

In the presence of the neck mass, the clinical diagnosis should begin with physical examination and thorough anamnesis, including the clinical history of the patient, toxic habits, antecedents of trauma or irradiation, uncontrolled food intake or recent travel to a tropical country. The time of appearance of the mass, its rate of growth and the presence of concomitant symptoms should also be evaluated.

The age of the patient is one of the main items in cervical tumefaction aetiology evaluation. Classically three age ranges have been established: pediatric (less than 15 years), young adults (16-40 years) and adults (over 40 years). The diagnosis of a neck tumefaction centers on specific aetiology depending on the age of the group involved. Thus, in pediatric patients and young adults adenopathies typically reflect the existence of congenital or infectious disorders, with increased prevalence of neoplastic lesions in the second group. On the contrary, among adults (over 40 years) attention should be paid to a neoplastic origin at first, and inflammatory pathology at the second place.

### *Physical examination*

The physical examination should determine the precise location and size of the neck mass, the possible presence of other tumefactions, and the existence of inflammation (3, 4). The exploration should be performed with slightly flexed neck of the patient, and all the cervical lymph node chains have to be palpated thoroughly. Pulsations or vibrations, as a response to palpation of a tumor mass, indicate a vascular origin of the adenopathy.

The age of the patient and the location of the tumefaction generally establish a differential diagnosis between adenopathy and other neck tumefactions. In pediatric patients and young adults, if cervical tumor is located in the midline or below the sternocleidomastoid muscle, with involving rapid growth and signs of inflammation, it is suggestive to congenital cervical mass.

On the other hand, a unilateral cervical tumefaction of an adult patient that is located at the trajectory of the lymph node chains, have rapid growth, size over 2 cm and no signs of inflammation, indicate a neoplastic lesion. Physical examination requires identification of the primary tumor in such cases. If adenopathies are bilateral, smaller, and detected in a young adult, the aetiological cause is typically inflammatory.

The physical examination findings, the location of the tumor, and the medical record of the patient will yield a probable diagnosis, although additional explorations are required to establish the definitive diagnosis (5, 6).

### *Additional necessary explorations*

Fine needle aspiration biopsy is the first procedure indicated after physical examination, and in most cases is sufficient for identification of the underlying aetiology (7). The technique involves use of a fine gauge needle to puncture the tumefaction and extract a sufficient number of cells to ensure a rapid histological diagnosis, producing only minimal discomfort for the patient. Multiple aspirations, correct puncture technique, and the expertise of the cytologist are essential presumptions for ensuring the maximal feasibility and reliability.

The largest margin of error corresponds to the differential diagnosis between lymphoma and thyroid papillary carcinoma, while the reliability of the technique approaches 100% in cases of malignant epithelial lesions. A biopsy with the Vim-Silverman needle is considered contraindicated because the risk of tumor cells seeding along the needle trajectory is suspected. This statement is ultimately questionable because surgical dissemination of malignancy by biopsy, rest of the tumor or palliative surgery is practically discarded. Fine needle aspiration biopsy was found particularly useful in the diagnosis of thyroid nodules (9, 10), and in the assessment of cyst aetiology. It could also be helpful for lymph node staging, aiming to plan adequate treatment modalities for oncological patients.

The ability of fine needle aspiration cytology to differentiate between carcinomas and lymphomas generally does not eliminate open biopsies, although in some cases facilitates prompt and adequate treatment (11).

Negative fine needle aspiration biopsy findings, particularly in adults with risk factors, do not allow us to discard the presence of malignancy; therefore repeated fine needle aspi-

rations are required, together with complementary tests, in order to rule out a neoplastic origin.

If definitive diagnosis of the adenopathy could not be established by physical examination and cytological finding, as well as in case of the discrepancies between the clinical characteristics and aspiration biopsy findings, imaging techniques could provide additional informations. Therefore, diagnostic imaging techniques allow visualization of the primary lesion, presence of additional adenopathies, assessment of their size and adhesion to tissue planes or structures, as well as other characteristics.

Computed axial tomography (CAT) and magnetic resonance imaging (MRI), which have relative advantages but also certain inconveniences, are yet the first choice imaging techniques, whilst additional exploration is scarcely needed.

Computed axial tomography (12, 13) provides a differential diagnosis between solid and cyst masses, establishes the location and extent of the lesion, the presence of calcifications, and its relations to the neighboring structures. The data obtained this way can also establish a possible glandular origin, and imaging with contrast delimit the blood flow. Cervical metastases are defined as adenopathies of 1.5 cm or larger, adenopathies with central necrosis, a group of three or more adenopathies having 8-15 mm in length, and the loss of tissue plane definition.

Distinguishing between solid and cyst masses could be accomplished by echosonography. If a differential diagnosis between an inflammatory and metastatic lymph node is necessary for staging, ultrasound is used for guiding the needle in fine needle aspiration cytology. Echo-Doppler exploration can also differ vascular masses from carotid involvement.

Magnetic resonance imaging (14-16) provides as many informations as CAT, or even more. In cases of metastases of unknown origin T2-weighted sequencing can localize incipient mucosal lesions. Contrast injection delimits major vessel involvement, and can replace arteriography for lesions at the base of the skull and in the upper third of the neck. Image resolution by MRI is generally greater than CAT image resolution. Multiplanar imaging can also be performed by MRI. A disadvantage of MRI is the possibility of artifacts caused by patient salivation or pulsatile vessel movements. Moreover, the MRI is more expensive and lasts longer than CAT diagnostics. It also has series of contraindications.

Angiography (17, 18) has gradually increased in importance with the elimination of technical problems. It is particularly indicated in patients with neck tumefactions suspected to a paraganglioma, but is also useful in the diagnosis of arterio-venous malformations, and in the evaluation of cervical tumor vascularization and the possible effects of tumors or traumatism upon the carotid artery. Selective pre-operative embolization can be carried out in hypervascularized masses, and in combination with CAT this technique can assess collateral arterial circulation in situations of internal carotid ligation.

Open surgical biopsy is indicated when imaging techniques and cytology fail to diagnose aetiology of the neck node metastasis. This generally occurs in patients with lymphomas, where an open biopsy is needed for histological labeling of the tumor despite fine needle aspiration positivity. (4, 11, 19, 20).

If biopsy implies an extensive cervical approach, a per-operative pathological diagnosis should be established, and in cases where a melanoma or carcinoma is diagnosed, cervical lymph nodes have to be removed during the same surgical procedure. In contrast, if an adenocarcinoma or lymphoma is identified at biopsy, the surgical wound should be closed and subsequent procedures undertaken (21).

### CERVICAL NEOPLASMS

Neoplastic pathology of the neck comprises two thoroughly distinct aetiologies: metastatic disease and lymphomas. Malignant lymphomas are lymphatic neoplasms that affect the lymphoreticular system. They account for 5% of all neoplasms generally, increasing to 55% among the pediatric population. The diagnosis is histological, and the processes are therefrom divided to Hodgkin and non-Hodgkin lymphomas. As to patient age at presentation, a bimodal curve, with a first peak at around 15-30 years, and a second peak at about age 50 is observed. A certain male predominance has been observed. The appearance of progressively growing lymph nodes without signs of inflammation is the primary symptom. Fever, nocturnal sweating, weight loss and pruritus are occasionally observed. The adenopathies are located in the neck in 60-80%, in the mediastinum in 60%, and in the abdominal cavity in 25% of cases, respectively. Thorough clinical examination and a biopsy are required to confirm a suspected lymphoma in the presence of a progressively growing neck tumefaction without inflammation in young patients, since carcinomas are unusual in this age group.

The appearance of lymphatic metastases depends on the histological grade of the tumor, the initial size of the lesion and the abundance of lymphatic capillaries within surrounding territories. While unilateral lesions spread to lymph nodes on the same side, the lesions in proximity to the midline, those affecting the lateral margin of the tongue, and the lesions in the nasopharynx can disseminate to both sides.

Metastatic adenopathy in an adult with an asymmetrical cervical mass measuring over 2 cm in diameter, with pain palpation, relatively rapid growth in the previous 3-4 months, and a history of smoking and alcohol intake is suspected. The diagnosis is confirmed by fine needle aspiration of the neck node. Also, a thorough clinical study, including careful examination of the skin in the regions of face, scalp and neck should be conducted. Furthermore, the oral cavity, nasopharynx, hypopharynx and larynx should be examined in search for the primary origin of the tumefaction. The patient study is in turn completed by imaging assessments (MRI or CAT) of the maxillofacial zone. However, despite these explorations, the primary cause of the adenopathy remains unestablished in 5% of cases (corresponding to metastases of unknown origin).

Predispositions for cervical metastases could be summarized as:

**Tumor location:** lesions in the floor of the mouth more frequently give rise to bilateral metastases, while tumors of the piriform sinuses and oral cavity show an increased tendency to develop occult metastases.

**Tumor stage:** the probability of lymphatic spread increases with primary tumor size.

**Histological grade:** a significant lack of tumor cell differentiation and the existence of perivascular and lymphatic invasion imply an increased risk of metastasis (21).

**Tumor cell ploidy:** recent studies have demonstrated that tumors with a high percentage of diploid DNA have increased aggressiveness, and hence a greater tendency to metastasize, (22).

**Patient immune status:** host immune function appears to play an important role in the phase of tumor spread (23).

Factors considered to determine worse if not the worst prognosis are:

**Lymph node positivity:** survival among patients with positive nodes decreases 50%. This correlation to decreased survival is also observed while analyzing patients with clinically positive nodes versus those without palpable adenopathies (24).

**Number of affected nodes:** survival was shown to decrease among patients with multiple positive nodes versus those with only one affected node - particularly when four or more nodes are involved. However, not all series confirm this (25).

**Location of adenopathy:** patients with positive nodes at inferior jugular and supraclavicular level have a poorer prognosis than with other locations involved.

**Bilateral adenopathies:** tumors of the oral cavity, oropharynx and hypopharynx with bilateral metastases imply a poorer prognosis. However, bilateral dissemination is only observed in 5% of head and neck tumors, particularly those of the base of the tongue, floor of the mouth, hypopharynx and supraglottic larynx. The appearance of contralateral metastases in a posterior phase has not been shown to imply a poorer prognosis than simultaneous bilateral presentations.

**Fixed adenopathies:** this factor interacts with others such as the number of affected nodes, their size and extracapsular invasion, since they mostly manifest simultaneously. However, in 30% of cases of lymph node fixation, no extracapsular spread is observed. Fixation to neighboring structures implies a two-fold greater recurrence rate than in patients with mobile adenopathies. Fixation is moreover a sign of non-operability, while fixation to large vessels suggests the need for radical treatment with possible preoperative patient management.

**Extracapsular invasion:** this was found to be the main factor influencing patient survival, and also associated to an increased recurrence rate. Extracapsular tumor spread is intimately linked to the size of the adenopathy. In this sense, while in 75% of those nodes measuring over 3 cm extracapsular invasion is present, only 14% of those having 1 cm in size also show extracapsular involvement. Three years survival in such cases is 15%, versus 33% among patients with positive nodes but no extracapsular infiltration.

If the primary tumor remains unidentified despite the diagnosis of metastatic adenopathy, and thorough clinical study with CAT or MRI imaging, then the metastasis is considered to be of unknown origin. Randomized biopsies of the nasopharynx, base of the tongue, tonsils and piriform sinuses are required in such cases, as these are regarded as the most likely sites of origin of such metastatic spread. The rationale for such biopsies is based on the theory of a sub-

mucosal origin of the primary neoplasm, where metastases occur at a very early stage. In patients with supraclavicular or low jugular adenopathies, the study must be complemented with bronchoscopy and esophagoscopy. Nevertheless, it has been estimated that only 20% of supraclavicular adenopathies originate from the aerodigestive tract, whilst the rest are attributed to the maxillofacial region.

The most common location of adenopathies of unknown origin is the jugulodigastric zone (50-70%), followed by the submaxillary and middle jugular regions. Approximately 45% are detected in stage N3, followed by stage N2 in 40%, and stage N1 in only 15% of cases. In terms of the histopathological diagnosis, squamous carcinoma is the

most frequent presentation (60%), followed by adenocarcinoma (22%) and a lesser prevalence of other tumor types, such as melanomas and anaplastic carcinomas.

The management of metastases of unknown origin is a matter of debate, and the lack of randomized series precludes establishing firm conclusions. In any case, the choice of treatment depends on the histology, stage and location of the lesion involved. The local lymph nodes metastasis should be removed during seeking for the primary tumor. In case of distal metastases presence (M1 status, stage IV), the only possible treatment is chemotherapy, if the overall condition of the patient permit such treatment. (26).

### Apstrakt

Metastatski limfni čvorovi u vratu su prvi simptom malignih bolesti u regionu glave i vrata kod 12% - 15% bolesnika. Tri različita faktora koja ukazuju na tri različita uzročnika ovih adenopatija su: kongenitalni, infektivni i neoplastični. Kod odraslih se prvo posumnja na neoplaziju. Inicijalna dijagnoza mora biti potvrđena citološkom dijagnozom iz uzorka dobijenog iglenom biopsijom, koja se zbog preciznosti izvodi pod kontrolom ultrazvuka ili rendgena. Ovim se podiže pouzdanost dijagnostike na više od 85%. Metastaze nepoznatog porekla čine više od 5% svih metastaza u vratu. Zbog toga su za dijagnostiku neophodne nasumične biopsije regiona za koje se sumnja na ranu diseminaciju. Lokalizacija, histološki tip, kao i stadijum bolesti i otkrivanje primarnog tumora su od ključnog značaja kao glavni prognostički faktor u navedenim slučajevima.

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