LITERATURE REVIEW

Head and neck cancers of unknown primary: A diagnostic and therapeutic challenge

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ABSTRACT

Head and neck cancers of unknown primary (CUP) represent up to 10% of all cancers located in the head and neck. True cancers of unknown primary, which remain of undetected primary origin after a correct clinical, imaging, surgical evaluation, have a reported frequency of between 1% and 2%. Cancers of unknown primary of the head and neck are a diagnostic challenge, considering that their main clinical manifestation is represented by the appearance of lymph node metastases in the cervical region.

In general, the detection of cancers with an unknown starting point is late, difficult, with significant therapeutic failure. The diagnostic-therapeutic approach starts from the histopathological structure of the lymph node metastasis and continues with a correct and complete imaging evaluation.

In this review are presented the diagnosis and therapeutic challenges and importance of head and neck cancers with unknown primary.

KEYWORDS: head and neck cancer, unknown primary, adenopathy, metastatic lymph node.

INTRODUCTION

"An adult patient who presents with a palpable lateral neck mass, whether solid or cystic, should be considered to have a metastatic lymph node until proven otherwise" stated Hayes Martin in 1961[1,2].

Head and neck cancers of unknown primary (CUP) represent up to 10% of all cancers located in the head and neck[3-5]. True cancers of unknown primary, which remain of undetected primary origin after a correct clinical, imaging, surgical evaluation, have a reported frequency of between 1% and 2%[2,4].

It can be stated that cancers of unknown primary of the head and neck are a diagnostic challenge, considering that their main clinical manifestation is represented by the appearance of lymph node metastases in the cervical region. Lymph node metastases may initially suggest a benign pathology, of viral or inflammatory etiology, which generally delays the diagnosis. For this reason, these cancers can have a poor prognosis. The lymph node biopsy and the histopathological structure, performed as early as possible, can establish the starting point of the lymph node metastasis in a proportion of 45-80%. The data reported in the specialized literature claim that up to 75% of head and neck cancers of unknown primary are squamous cell carcinomas[3,4,6], in 45% of cases the primary tumor being identified at the level of the palatine tonsil fossa and in 44% at the level of the tongue base[7,8]. However, the rate of undetected primary tumor can vary between 5% and 50%[9].

In general, the detection of cancers with an unknown starting point is late, difficult, with significant therapeutic failure. The diagnostic-therapeutic approach starts from the histopathological structure of the lymph node metastasis.

HISTOPATHOLOGY OF THE HEAD AND NECK CUP

From a histopathological point of view, head and neck cancers can have the following structures: squamous cell carcinomas (epidermoid carcinoma, adenocarcinoma, undifferentiated carcinoma), thyroid carcinomas, neuroendocrine

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Table 1. Classification of cervical lymph node chains and cervical lymph node metastasis in head and neck cancers (according to AAO-HNS[12]).

Lymph node chain	Location	Primary tumors with cervical lymph node metastasis
Ia	Submental	Oral cavity, lips
Ib	Submandibular	Oral cavity, submandibular gland, the anterior part of the nasal cavity
II	Upper jugular	Oral cavity, oropharynx, hypopharynx, nasopharynx, parotid, larynx, nasal cavity
III	Middle jugular	Oro-, hypo- and nasopharynx, larynx, oral cavity
IV	Lower jugular	Oro-, hypo- and nasopharynx, the cervical segment of the esophagus, thyroid, urogenital tract, liver, pancreas
Va	The upper part of the posterior lymph node triangle (Spinal accessory lymph nodes)	Thyroid, salivary glands, nasopharynx
Vb	The lower part of the posterior lymph node triangle (Transverse cervical nodes and the supraclavicular nodes)	Thyroid, nasopharynx, gastrointestinal tract, urogenital tract, liver, pancreas
VI	Anterior compartment	Thyroid, larynx, hypopharynx, the cervical segment of the esophagus
Subclavicular		Thyroid, metastases of non-head and neck tumors

carcinomas, salivary gland carcinomas, carcinomas of subclavicular origin. Starting from these structures, we must look for the primary tumor from which the cervical lymph node metastasis started.

Squamous cell carcinoma

Squamous cell carcinoma (SCC) is the most frequently incriminated in the histopathology of head and neck CUP, its frequency being between 53% and 77%[9,10]. Of these, approximately 58% represent the common form of SCC, 15% being represented by adenocarcinomas, undifferentiated carcinomas, seromucous, basaloid or papillary carcinomas[10,11].

The cervical lymphatic metastasis of a squamous cell carcinoma can start most frequently from the level of the upper aerodigestive tract, followed by malignant tumors from the level of the thyroid gland, salivary glands, skin, neuroendocrine structures. They mainly involve cervical lymph node chains I, II, III, Va, according to the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) classification[12] (Table 1). Lymph node chains IV, Vb can be involved in the dissemination of tumors of the thyroid gland, of the gastrointestinal and urogenital tract, liver and pancreatic tumors, lung or genital tumors[12].

According to this information, lymph node metastasis of head and neck cancers can be summarized as follows: oropharyngeal SCC in cervical lymph node chains II, III, IV; nasopharyngeal SCC in V and retropharyngeal ganglia; salivary gland tumors in IIb; thyroid gland tumors in VI[6,13].

These details are particularly important when facing a cervical adenopathy mass, considering that up to 90% of squamous cell carcinomas that initially present as tumors of unknown primary origin are located at the oropharyngeal level, followed by nasopharyngeal and hypopharyngeal ones[7,10]. The preferred location at the oropharyngeal level, namely the palatine tonsils and the base of the tongue, seems to be due to the lympho-epithelial structure of these entities. In an immunosuppressed patient, a deep, millimetric, imperceptible cancerous lesion quickly produces cervical lymph node metastases, also favoured by a highly developed vascular and epithelial structure. For this reason, in the case of palatine tonsil cancer, the notion of "in situ" carcinoma is improperly used.

An important association of SCC is with Human Papillomavirus (HPV), especially in the case of oropharyngeal cancer. According to literature, approximately 80% of SCC manifested as CUP of the head and neck are associated with the presence of HPV (in 34% of patients, the primary tumor is located in the oropharynx)[10,14,15], the increase in the incidence of this association being by 225% in recent years[6,16,17]. As for nonkeratinizing squamous cell carcinoma with nasopharyngeal localization, it has been shown to be more frequently associated with the presence of the Epstein-Barr virus (EBV)[10].

Thyroid carcinoma

Thyroid carcinomas are generally papillary carcinomas with a high degree of metastasis in the cervical lymph nodes. Their presence is associated with high levels of thyroglobulin or calcitonin, in the case of medullary carcinoma[10,18,19].

Neuroendocrine carcinomas

The most frequent localization of neuroendocrine carcinomas in the head and neck is at the supraglottic level. Another primary location can be the skin, since Merkel

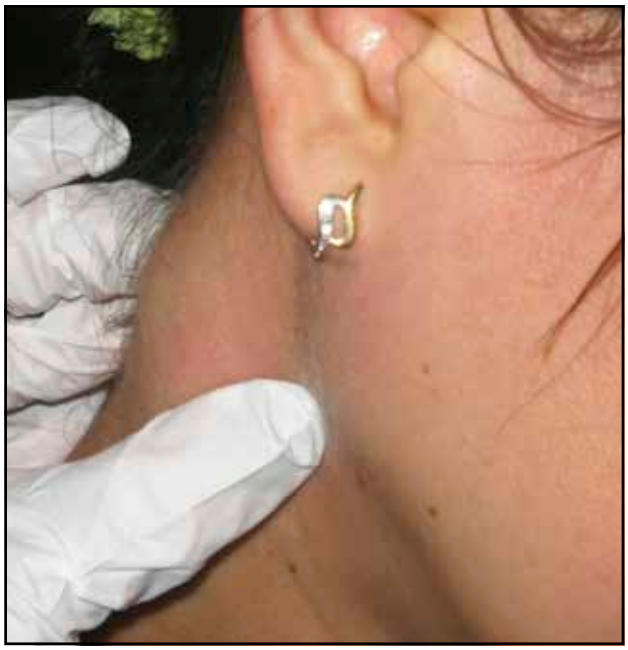

Figure 1. Laterocervical lymphadenopathy.

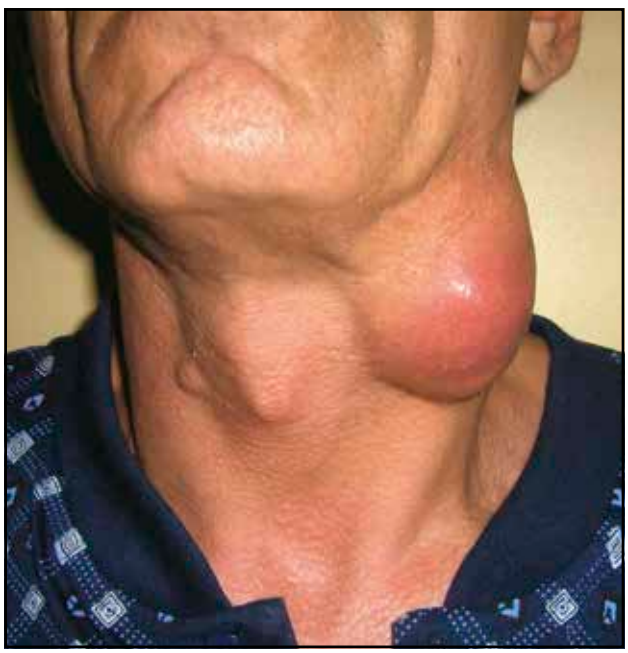

Figure 2. Left laterocervical metastatic adenopathy (N3) – nasopharyngeal carcinoma.

carcinoma can metastasize to the cervical lymph nodes and is characterized by the presence of cytokeratin 20[10,20].

Adenocarcinoma of the salivary glands must be taken into account and investigated in the case of metastatic adenopathy involving the cervical lymph node chains I, II, III[10,21].

Malignant tumors (carcinomas) located in the subclavicular organs are responsible for approximately 1% of cervical lymph node metastases, being represented by primary tumors located in the breast, lungs, kidneys, testicles, uterus or ovary[22].

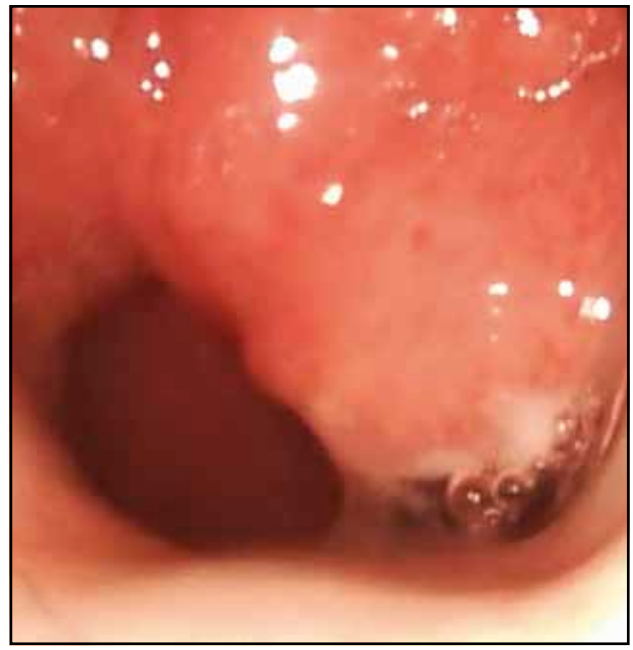

Figure 3. Nasopharyngeal tumor (endoscopic view).

Supraclavicular adenopathy occurs 4-5 months after the onset of primary tumors of the head and neck or distant organs. Regardless of the origin of the adenopathy, the ENT clinical examination is usually done 3-5 weeks after the appearance. In 95% of cases, it is not painful, the reason for the first consultation being the increase in size of the lymph nodes. Clinically, it can be easily confused with a branchial cleft cyst, therefore a thorough evaluation is important to establish a quick and correct diagnosis.

THE DIAGNOSIS ALGORITHM IN UNKNOWN PRIMARY OF THE HEAD AND NECK

Clinical examination and anamnesis

A cervical adenopathy older than 3 weeks may suggest a primitive cancer, inflammation, salivary disorder or viral or bacterial infection.

The most common form of presentation is cervical swelling older than 3 weeks, in approximately 94% of cases being the only symptom[23]. This can be associated with dysphagia, odynophagia, unilateral otalgia, nasal obstruction, repeated episodes of epistaxis. Weight loss was reported in less than 7% of patients with this pathology.

In these patients, the identification of risk factors is very important: male, over 40 years old, smoker, alcohol user, sexual habits, socio-economic status. However, in recent years, with the increase in the incidence of HPV infection, the characteristics of the "new" patient with head and neck can-

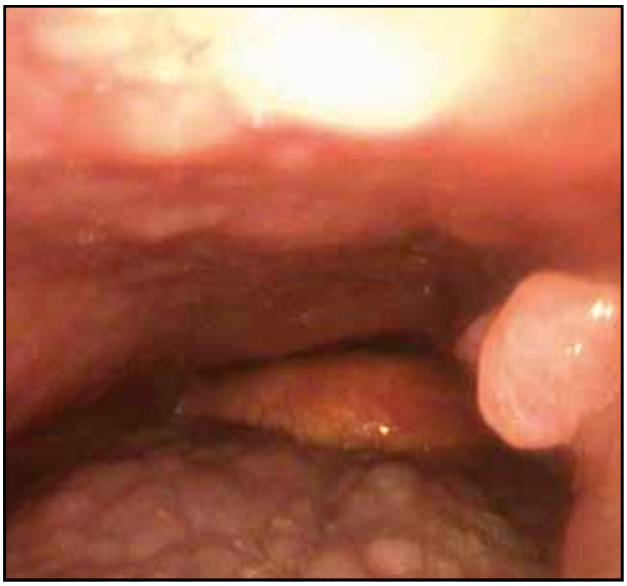

Figure 4. Oropharyngeal non-keratinizing infiltrative squamous cell carcinoma (endoscopic view).

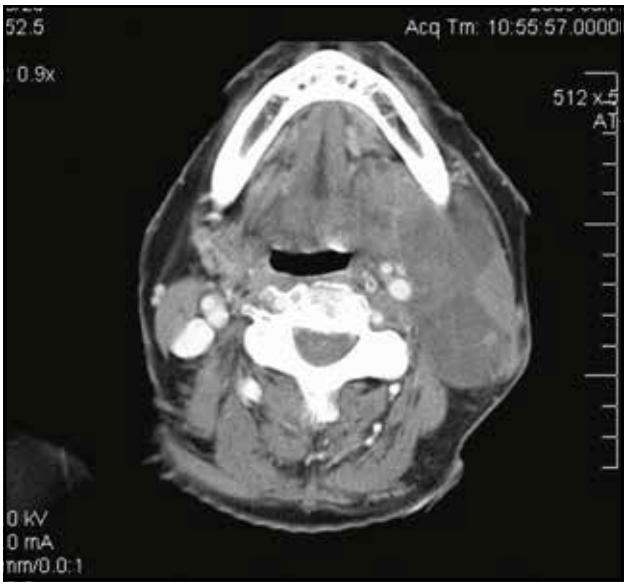

Figure 5. Left cervical malignant lymphadenopathy in a patient with nasopharyngeal carcinoma (cervical CT scan, axial slice).

cer are mostly male, non-smokers, non-drinkers of alcohol, under 40 years of age, with multiple sexual partners[16,24]. Palpation of the cervical region (Figure 1) can give certain suggestive information for the malignant nature of the adenopathy: hard tumor formation, fixed to superficial and deep planes, the skin at its level being modified in appearance and consistency[24] (Figure 2).

The endoscopic examination, rigid and/or flexible, with the evaluation of the nasopharynx (Figure 3), the base of the tongue, the hypopharynx, the larynx, must necessarily be part of the evaluation of such a patient (Figure 4). An important role begins to be played by fibroscopy with narrow band imaging (NBI), which allows the visualization of neo-angiogenesis, of the intense vascularization of a cancerous tumor area. According to the literature, NBI endoscopy has a detection rate of up to 35%, a sensitivity of 83% and specificity of up to 88%[25,26].

Imaging evaluation

Ultrasound of the cervical soft tissue allows the differentiation of solid masses from cystic ones, the evaluation of the thyroid gland, but it can be useful in the puncture of the ganglion mass.

The computed tomography (CT) examination of the cervical region performed with contrast agent should be, according to the recommendations of the American Society of Clinical Oncology (ASCO), the first recommendation for imaging evaluation in the case of patients with suspected cervical lymph node metastasis[24] (Figure 5, Figure 6). With a

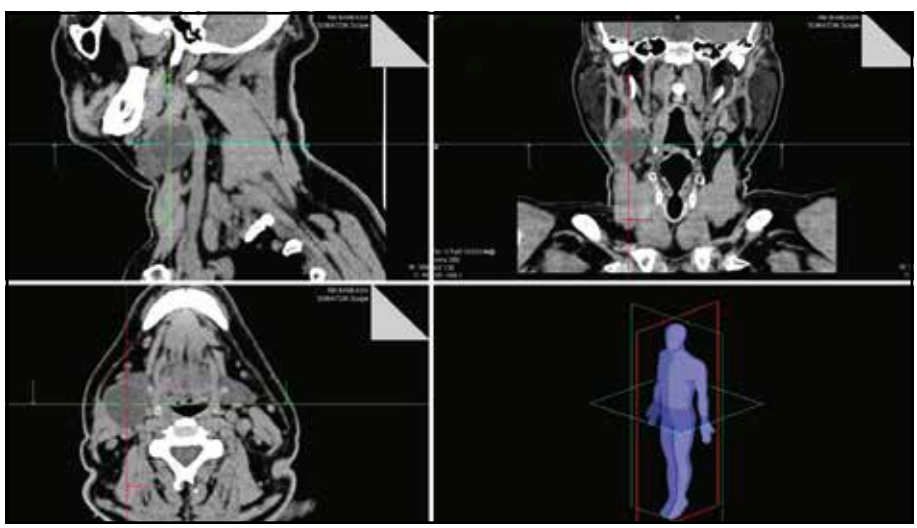

Figure 6. Cervical CT scan (sagittal, coronal, axial slices) – right cervical lymph node mass.

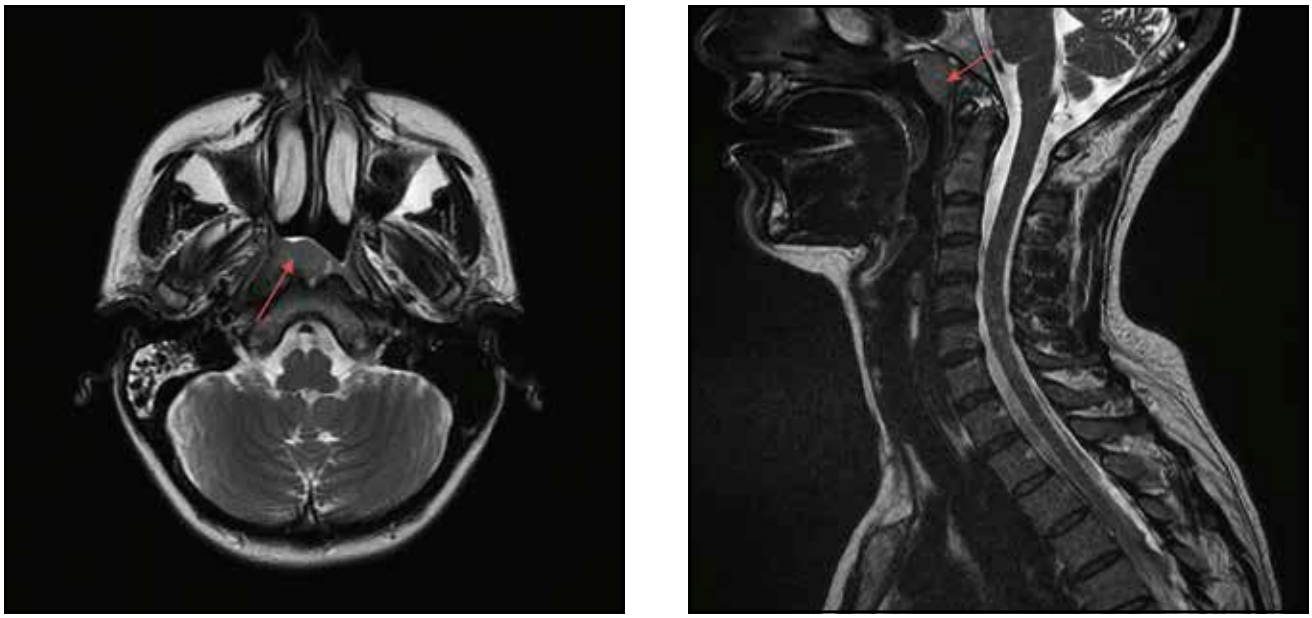

Figure 7. Cranial and neck MRI scan (axial and sagittal slices) – nasopharyngeal tumor (arrows).

sensitivity between 49-94% and a specificity of 78-98%[27], the CT is recommended before performing the biopsy, as it can provide important information about the tumor extension, consistency, the relationship of the tumor formation with the neighbouring structures (muscles, blood vessels, nerves). Nuclear magnetic resonance imaging (MRI) of the cervical region with contrast agent can be useful in detecting a small oropharyngeal tumor formation or nasopharyngeal tumor (Figure 7). Compared to CT, MRI evaluation proved to have higher specificity but lower sensitivity[28].

In those patients in whom neither the clinical examination nor the CT exam reveals the primary tumor, the PET-CT (18F-fluorodeoxyglucose-positron emission tomography) evaluation represents the next step in the assessment according to the ASCO guidelines[24]. Although its diagnostic value is limited by tumors smaller than 10 mm, although it can give both false-positive and false-negative results, PET-CT has a reported sensitivity between 27-91.5%[10,17], a specificity of 70.4-87%[17], with a detection frequency of the primary tumor varying between 17 and 55.2%[17]. False-positive results can occur at the level of the lympho-epithelial tissue of Waldeyer's ring, which physiologically has an increased capacity to capture fluorodeoxyglucose, but also at the level of the salivary glands[10]. Sokoya et al. reported a sensitivity of 73.1% and a negative predictive value of 68.9% of PET-CT in the detection of CUP of the head and neck, the most frequent locations of the primary tumor being the palatine tonsils (56%), base of the tongue (25%), nasopharynx (3%), hypopharynx (3%)[29]. On the other hand, according to the results published by Han et al.[30], PET-CT helped to detect the primary tumor in 42.5% of the evaluated patients, with an accuracy of 88.3%, specificity of 85.2% and sensitivity of 91.5%. At the same time, Deonarine et al.[31] claim in a study published in 2013 that the primary tumor was detected by PET-CT in 37.3% of the patients included in the study, 54.9% of occult metastases, with a specificity of 70.4%, sensitivity of 79.2% and an accuracy of 74.5%.

Biological laboratory samples

Routine analyses, such as blood count, erythrocyte sedimentation rate, fibrinogen, C-reactive protein, can identify the existence of an infectious and/or inflammatory process.

Tests for the identification of certain parasites, such as Immunoglobulin (Ig) G, IgM for toxoplasmosis, toxocariasis, can help in establishing the etiology of lymph node inflammation.

Laboratory blood tests for the detection of EBV (Epstein-Barr virus), HIV, CMV (cytomegalovirus), as well as thyroid hormone values can help in establishing the location of the primary tumor in the case of a CUP of the head and neck.

The cytological examination of the material obtained by fine needle biopsy or core needle biopsy can identify the histological type of lymph node metastasis.

Fine needle aspiration biopsy (FNA) performed under ultrasound guidance is a minimally invasive technique, safe and easy to perform; it has a specificity in the case of lymph node metastases of up to 96.9% and a sensitivity of up to 94.2%[32]. It has also proven to be useful in puncturing thyroid nodules (79.7% sensitivity, 98.1% specificity), salivary glands (85.5% sensitivity, 98.4% specificity), or oral lesions and cystic formations (78.8% sensitivity, 97% specificity)[32]. There are also cases (10-15% reported by Ye et al.[28]) in which the material obtained is not sufficient to provide an accurate diagnosis, at which point excisional biopsy is recommended.

Core needle biopsy (CNB) consists in the use of a piston through which a larger fragment of tissue can be sampled

Table 2. TNM classification and staging in head and neck CUP without identification of the primary tumor, according AJCC[35].

TNM classification		
Primary tumor (T)		
T0		The primary tumor cannot be identified
Cervical lymph nodes (N)		
Clinical classification (cN) - patients in whom cervical dissection was not performed		
cNx		Cervical lymph nodes cannot be evaluated
cN0		No metastases in the cervical lymph nodes
cN1		Involvement of a single ipsilateral lymph node, less than or equal to 3 cm, without extranodal extension (ENE(-))
cN2	cN2a	A single lymph node, larger than 3 cm but smaller than 6 cm, ENE(-)
	cN2b	More ipsilateral lymph nodes, smaller than 6 cm, ENE(-)
	cN2c	Multiple bilateral or contralateral lymph nodes, smaller than 6 cm, ENE(-)
cN3	cN3a	One lymph node, larger than 6 cm, ENE(-)
	cN3b	Involvement of any lymph node, ENE(+)
Pathological classification (pN) - patients who underwent cervical dissection		
pNx		Cervical lymph nodes cannot be evaluated
pN0		No metastases in the cervical lymph nodes
pN1		Involvement of an ipsilateral node, smaller than or equal to 3 cm, ENE(-)
pN2	pN2a	An ipsilateral node, smaller than or equal to 3 cm, ENE(+) or an ipsilateral node, smaller than 6 cm and larger than 3 cm, ENE(-)
	pN2b	More ipsilateral lymph nodes, smaller than 6 cm, ENE(-)
	pN2c	More contralateral or bilateral lymph nodes, smaller than 6 cm, ENE(-)
pN3	pN3a	A lymph node larger than 6 cm, ENE(-)
	pN3b	A lymph node larger than 3 cm, ENE(+) or multiple ipsilateral, contralateral or bilateral lymph nodes, of any size or a contralateral node, of any size, ENE(+)
Distant metastases (M)		
cMo		No distant metastases
cM1		Present distant metastases
pM1		Present distant metastases, microscopically confirmed

STAGING			
T	**N**	**M**	**Stage**
T0	N1	M0	III
T0	N2	M0	IVA
T0	N3	M0	IVB
T0	N1-3	M1	IVC

Table 3. TNM classification and staging of CUP of head and neck with primary tumor at nasopharyngeal level by positive EBV test, according to AJCC[35].

TNM classification			
Primary tumor (T)			
T0	The primary tumor cannot be identified, positive EBV test in the lymph node biopsy		
Cervical lymph nodes (N)			
Nx	Cervical lymph nodes cannot be evaluated		
N0	No metastases in the cervical lymph nodes		
N1	Unilateral involvement of one or more lymph nodes and/or metastasis in unilateral/bilateral retropharyngeal nodes, smaller than 6 cm, located above the caudal margin of the cricoid cartilage		
N2	Bilateral involvement of lymph nodes, smaller than 6 cm, located above the caudal margin of the cricoid cartilage		
N3	Unilateral or bilateral lymph nodes, larger than 6 cm, and/or extension under the caudal margin of the cricoid cartilage		
Distant metastases (M)			
cMo	No distant metastases		
cM1	Present distant metastases		
pM1	Present distant metastases, microscopically confirmed		
STAGING			
T	**N**	**M**	**Stage**
T0	N1	M0	II
T0	N2	M0	III
T0	N3	M0	IVA
T0	N1-3	M1	IVB

and has a reported diagnostic accuracy of up to 94%, with a sensitivity of 92% and specificity of 100%[33].

The biopsy material obtained both by FNA and by CNB can be used to identify the p16 marker for the HPV E7 oncogene by immunohistochemistry, thyroglobulin dosage in case of suspicion of a tumor in the thyroid gland, EBV identification or HPV/EBV RNA identification by in situ hybridization.

The excisional biopsy may involve the adenopathy and/or the tumor lesion identified at the naso-, oro-, hypopharyngeal or laryngeal level. The surgical specimen is sent for histopathological examination completed with immunohistochemistry tests.

Ipsilateral tonsillectomy with tongue base biopsy can detect the primary tumor in 18-45% of cases[10]. If transoral robotic surgery (TORS) is used in this process, the detection rate of the primary tumor can increase up to 94%[10]. Another advantage is the possibility of diagnosing and resecting the tumor in the same session, the risks of the procedure being represented by bleeding (0.5-10%), dysphagia, edema, death.

STAGING OF HEAD AND NECK CANCERS OF UNKNOWN PRIMARY

Starting from 2017, the American Joint Committee on Cancer (AJCC) included head and neck tumors of unknown primary in the TNM staging (T – tumor, N – lymph nodes, M – metastasis), also taking into account the association or non-association with HPV in the case of oropharyngeal carcinomas[34,35]. In the case of CUP, T0 cannot be associated with a specific anatomical area for the primary tumor. According to data from the literature, over 90% of T0 in CUP of the head and neck are associated at immunohistochemical tests with HR-HPV or EBER (Epstein-Barr-encoded RNA)[34]. In these cases, the site of the primary tumor can be established either at the oropharyngeal level for T0 with HR-HPV positive or nasopharynx for T0 with EBER positive. Depending on the possibility of identifying the primary tumor and depending on the presence of the HPV/EBV virus, TNM classifications and staging were developed (Tables 2-4).

Table 4. TNM classification and staging of CUP of head and neck with primary tumor at oropharyngeal level by positive HR-HPV test, according to AJCC[35].

TNM classification			
Primary tumor (T)			
T0	The primary tumor cannot be identified, positive HR-HPV test in the lymph node biopsy		
Cervical lymph nodes (N)			
Clinical classification (cN) - patients in whom cervical dissection was not performed			
cNx	Cervical lymph nodes cannot be evaluated		
cN0	No metastases in the cervical lymph nodes		
cN1	One or more ipsilateral nodes, smaller than 6 cm		
cN2	Lymph nodes located contralaterally or ipsilaterally, smaller than 6 cm		
cN3	Lymph nodes larger than 6 cm		
Pathological classification (pN) - patients who underwent cervical dissection			
pNx	Cervical lymph nodes cannot be evaluated		
pN0	No metastases in the cervical lymph nodes		
pN1	Metastases in 4 or fewer lymph nodes		
pN2	Metastases in more than 4 nodes		
Distant metastases (M)			
cMo	No distant metastases		
cM1	Present distant metastases		
pM1	Present distant metastases, microscopically confirmed		
STAGING			
T	**N**	**M**	**Stage**
T0	N1	M0	I
T0	N2	M0	II
T0	N3	M0	III
T0	N1-3	M1	IV

HEAD AND NECK CUP TREATMENT

According to the NCCN (National Comprehensive Cancer Network) guidelines, the treatment of head and neck cancer of unknown primary is based on the location of the primary tumor, if it has been detected, and on TNM staging[36]. Depending on these details, we can talk about surgical and/or oncological treatment. Surgical treatment is indicated in adenocarcinomas, neuroendocrine tumors, as long as the primary tumor is detected, followed by adjuvant radiotherapy treatment[24,36].

The first step in the treatment of CUP of the head and neck depends on the result of the FNA cytological examination of the cervical adenopathy: 1. if a SCC, adenocarcinoma, neuroendocrine or undifferentiated carcinoma is found, the treatment must take into account staging, the presence or absence of HPV/EBV infection and the identification of the location of the primary

tumor; 2. result suggestive of lymphoma, thyroid gland tumor or melanoma, one should follow the indications in the treatment guidelines for these pathologies[36]. If the primary tumor is identified, the patient will be treated according to the therapeutic protocols for each individual location.

Principles of treatment for squamous cell carcinomas, adenocarcinomas, undifferentiated or neuroendocrine carcinomas

According to NCCN guidelines[36], an adenocarcinoma, SCC, undifferentiated carcinoma, neuroendocrine carcinoma, in stage T0 associated with positive p16-HPV should be treated as an oropharyngeal cancer[37], and if it is associated with positive EBV / positive EBER, it must be treated as a nasopharyngeal cancer[38]. In T0 head and neck CUP, positive p16-HPV, one can opt for ipsilateral or bilateral cervical lymph node dissection followed by radiotherapy or concurrent systemic therapy/radiotherapy or induction chemotherapy followed by radiotherapy or concurrent systemic therapy/radiotherapy. In T0 head and neck CUP, positive EBV / positive EBER, depending on the presence of lymph node metastases and distant metastases, the therapeutic scheme may include: radiotherapy only, radiotherapy with/without concurrent systemic therapy/ radiotherapy, induction chemotherapy followed by systemic therapy/radiotherapy. In cases with distant metastases present (M1), regardless of the nodal stage (N0-3), one can opt for: systemic therapy associated with radiotherapy or cisplatin/radiotherapy, systemic therapy, concurrent treatment with cisplatin and radiotherapy.

Principles of treatment in CUP of the head and neck without identification of the primary tumor

If the primary tumor could not be identified, depending on the cervical lymph node chain involved in the metastasis, the treatment is established. An adenocarcinoma involving cervical lymph node chains I-III, with negative test of thyroglobulin and calcitonin, will require surgical intervention for cervical lymph node dissection with or without parotidectomy, followed by radiotherapy in the cervical region with/ without the parotid area. The involvement of IV, V cervical lymph node chains requires subclavicular evaluation to identify the primary tumor, with or without cervical lymph node dissection plus adjuvant treatment.

In case of a lymph node histopathological result suggestive of squamous cell carcinoma, poorly differentiated or nonkeratinizing or anaplastic SCC, the treatment should be recommended depending on the stage of lymph node metastasis[36]. In stage N1, cervical lymph node dissection or radiotherapy can be performed, and in stage N2, cervical dissection or concurrent systemic therapy/radiotherapy or induction chemotherapy followed by systemic therapy/radiotherapy.

A particularly important piece of information in the treatment choice is given by the result of the cervical dissection. In stage N1 without extranodal extension, radiotherapy proved to have good control over local evolution and survival[39]. Also in these cases, one can only opt for keeping the patient under observation, with periodic clinical and imaging assessment of the head and neck. An N2, N3 without extranodal extension can be treated by radiotherapy or systemic therapy/radiotherapy. The presence of extranodal extension requires as a first step systemic therapy/radiotherapy or just radiotherapy, depending on the tumor volume, the lymph node involved, the status of HPV/EBV infection.

Principles of radiotherapy treatment

The choice of the type and scheme of radiotherapy treatment (target, dose, fractionation with or without chemotherapy) depends on the tumor characteristics, location, and, in this case, on the presence or absence of viral infection with HPV or the Epstein-Barr virus. The most used form of radiotherapy at the moment is intensity modulated radiotherapy (IMRT) which, together with other techniques such as proton beam therapy (PBT), volumetric modulated arc therapy (VMAT), tomotherapy, image-guided radiotherapy (IGRT), has the advantage of protecting important, vital organs in the immediate vicinity of the target area (for example, the brain, cochlea, optic chiasm, etc.)[36]. If radiotherapy is recommended to be done postoperatively, the duration between the two must be no more than 6 weeks[40].

In the case of CUP of the head and neck, with or without identification of the primary tumor, radiotherapy is indicated once a day, 5 days a week, for 6-7 weeks. The dose and the target area depend on the location of the lymph node tumor and the location of the primary tumor. In case of oropharyngeal location of the primary tumor or p16-HPV positive at FNA of the lymph node mass, a dose between 66Gy and 70Gy is recommended, and postoperatively it can vary between 60Gy and 66Gy[36]. In the case of nasopharyngeal primary location or EBV positive at FNA of the lymph node mass, doses of 70-70.2Gy are recommended in high-risk cases (primary tumor, lymph node metastasis) and doses of 44-50Gy up to 54-63Gy in low-risk or intermediate cases. In cases where the primary tumor is not identified, radiation therapy aimed at the cervical region is dosed fractionally, 66-70Gy.

The combination of radiotherapy with systemic therapy, respectively chemotherapy as a competitive therapy, involves the fractionated use of 70Gy for 7 weeks, with the administration of cisplatin every 3 weeks (2-3 cycles of chemotherapy)[41]. If carboplatin or 5-fluorouracil is used, standard fractionation with 3 cycles of chemotherapy is recommended[42].

Principles of systemic chemotherapeutic treatment

The choice of systemic chemotherapeutic treatment must be made according to the characteristics of each individual patient. The most common combination in clinical practice is cisplatin with radiotherapy, whether the primary tumor is identified or not, both before and after surgery[24,36,43]. Other substances that can be used are carboplatin or 5-fluorouracil. In the induction therapy, the most used are docetaxel, cisplatin, 5-FU, or gemcitabine in the case of involvement of the nasopharynx[24,36,44,45].

PROGNOSIS OF HEAD AND NECK CANCERS OF UKNOWN PRIMARY

The prognosis of CUP of the head and neck can be influenced by many factors. The positive prognosis was associated with young age and especially the association with the presence of HPV. Smoking patients, known as alcohol consumers, extranodal extension and the absence of HPV infection have been shown to have a negative prognosis[46].

Axelsson et al.[46], in a study conducted between 1992-2009, showed a 5-year survival of 88% in patients with p16-HPV positive tumors, compared to 61% in p16-HPV negative tumors. In a retrospective study, Sivars et al. observed a significantly increased survival rate at 5 years in the case of p16-HPV positive head and neck CUP compared to p16-HPV negative ones, 80% versus 36.7%[47]. The same results were confirmed by Cheraghlou et al., with a 3-year survival of 94.8% in HPV-positive cases and 80.3% in HPV-negative cases[48].

Also, the choice of radiotherapy as the only therapy in cN2, N3 cases seems to be associated with a poor prognosis in terms of survival compared to multimodal chemotherapy treatment or associated with surgery[9,48].

CONCLUSIONS

Head and neck cancers of unknown primary origin represent a challenge both from a diagnostic and therapeutic point of view, and unfortunately approximately 50% of cases are diagnosed late.

It is important for the doctor to use all clinical and paraclinical methods for the diagnosis and early detection of the tumor. A positive p16-HPV cancerous tumor should direct the doctor towards an oropharyngeal cancer located at the level of the palatine tonsil or the base of the tongue, and a positive EBV/EBER result should force a careful evaluation of the nasopharynx.

The multimodal treatment must be individualized depending on the type of tumor, location, extension, detection or not of the primary tumor, the association or not of the HPV/EBV viral infection, and may consist of radiotherapy, associated or induction chemotherapy and surgical treatment in selected cases.

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