

Review

Advancement in the Oropharyngeal Primary Unknown Cancer Diagnostic and Current Treatments Pathway: A Narrative Review

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Abstract: **Objective:** The objective of this article is to define a correct diagnostic pathway for oropharyngeal cancer of unknown primary (OPCUP) identification. **Background:** OPCUP represents one of the most frequent causes of neck metastases onset without the identification of the primary tumor. Therefore, there is a high percentage of late or missing diagnoses, resulting in treatment delay or in a wrong therapeutic process. The up-to-date diagnostic procedures can help us to begin therapies at the right time. **Methods:** This is a review of the latest articles about diagnostic pathways in the OPCUP. A selection of the references was carried out in PubMed, EMBASE, Cochrane, and CENTRAL electronic databases. **Conclusion:** The oropharynx represents the most common site of primary unknown head and neck cancer (HNCUP). Recent epidemiologic data reported an increasing incidence of HNCUP related to human papilloma virus positive squamous cell carcinoma. Positron emission tomography combined with computerized tomography scanning or magnetic resonance imaging allows for improving the detection of primary unknown tumors and distant and locoregional metastases. Finally, the introduction of the trans-oral robotic surgical approach has introduced a new role of surgery in the HNCUP diagnosis and treatment. Hence, the new technological improvement allows reaching in most HNCUP patients an early diagnosis, achieving targeted management and better treatment outcomes, as well as decreasing toxicity and the side effects of treatment options.

Keywords: oropharyngeal primary unknown cancer; neck masses; NBI; Us-FNAC; Us-FNAB; E6/E7 mRNA; PET-CT; TLM; TORS



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1. Introduction

Over the past three decades, the incidence of oropharyngeal cancer (OPC) has increased in western countries due to the higher incidence of human papilloma virus (HPV) infection, which is identified as the major etiological agent of oropharyngeal squamous cell carcinoma (OPSCC) [1,2]. In Asian countries, the incidence of HPV-related cancers is low: around 45% in Japan and only 30–40% in Taiwan or Korea [1,2]. The first clinical presentation of OPSCC-HPV-positive tumors is frequently characterized by small volume primary lesions and large nodal masses.

Unknown primary tumors in the head and neck district occur with an incidence between 3 and 9%, and squamous cell carcinoma (SCC) is found in 53–77% of the patient population [2].

The onset of a cervical mass due to enlarged lymph nodes is the most frequently reported as the first clinical presentation. The 5-year survival rate of unknown oropharyngeal primary ranges from 35 to 50%, and its outcome is more favorable if the primary tumor is detected [3].

OPC of unknown primary (OPCUP) represents one of the most frequent causes of neck metastases onset without the identification of the primary tumor. Hence, the diagnostic strategy for the primary tumor represents a key role in prognosis and treatment planning [4–6]. Recently, technological improvements in diagnostic work-up, as well as a therapeutic strategy, improved the percentage of OPCUP identification, optimized targeted management and treatment outcomes, as well as decreased toxicity and the side effects of treatment options.

In this narrative review, we present an up-to-date review of the latest advances in the diagnostic work-up of OPCUP.

2. Methods

A comprehensive review of the English language literature on upper airway surgery for OPSCC diagnosis was performed. A selection of the references was carried out in PubMed, EMBASE, Cochrane, and CENTRAL electronic database from 1990 up to March 2021 using the search following keywords: “oropharyngeal primary unknown cancer” OR “neck masses” OR “Us-FNac” OR “Us-FNab” OR “NBI” OR “PET-CT” combined with the use of the AND function with “oropharyngeal primary unknown cancer” OR “early detection” OR “diagnosis” OR “Histopathology” OR “CT” OR “MRI” OR “PET” to better select the research. In order to further reduce the risk of incomplete literature analysis, a manual search through the bibliography of the included papers was carried out. Systematic reviews, meta-analyses, and international guidelines were the preferred categories of articles searched. A total number of 36 papers were selected for review by means of the analysis of the keywords in the title and in the abstract text.

2.1. Physical Examination

The clinical presentation of a patient with OPC of unknown primary (OPCUP) is related to their social history.

There are two categories of patients who are usually involved:

(1) The first group is represented by HPV-negative subjects; predominantly male (69.2 male vs. 30.8 female); >60 years old; related to tobacco abuse, alcohol abuse, betel nut chewing abuse, and poor dentition; and low socioeconomic status. In addition HPV negative subjects, oropharyngeal cancer can occur in relatively young patients with no history of tobacco and alcohol abuse; in these cases, etiology is unclear [1];

(2) The second group is represented by HPV-positive subjects, younger than in group one, predominantly males (76% male vs. 23% female), with multiple sexual partners (especially oral sex encounters), no strong association with tobacco, alcohol abuse or poor dentition, and higher socioeconomic status. This category has better clinical outcomes in overall survival (80.89% vs. 37.08%) [2].

Patients usually present with medium or large cervical masses with 3–4 weeks progression, more frequently located in level II (75%) followed by level III, I, and less frequently, level IV [3].

The palpable neck mass may be firm or cystic with a tense or soft consistency. On careful questioning, the patient may experience referred symptoms from the head and neck primary lesion, such as a sore throat when swallowing, ear pain, new nasal obstruction, and voice change.

Nevertheless, the adult patient population complaining of a palpable lateral neck mass, whether solid or cystic, should be considered to be a metastatic lymph node until proven otherwise by the diagnostic work-up [4].

Clinical N classification at diagnosis is usually N2/N3. In 90% of cases, a cervical lymph node mass is the only symptom in 90% of cases, followed by pain and weight

loss. Unfortunately, the diagnosis time of OPCUP from the onset of the cervical mass is about 3 months [3,7]. The diagnostic approach starts with an accurate patient history. The examination must be performed with consideration of all possible primary cancer sites, guided by the level of lymph node involvement (expected lymphatic drainage patterns) [8]. Palpation of each possible primary site is important, especially for palatine tonsils and tongue base [9].

Thereafter, a fibroscopy of the upper aerodigestive tract is performed, which can be complemented by Narrow Band Imaging (NBI) or other advanced techniques such as Professional Image Enhancement Technology PIET SPECTRO. The shifting of the color spectrum made by restricting wavelength through two optical filters (blue filter 415 nm e green filter 540 nm) can show structures with greater differentiation. In particular, they have the ability to identify neoangiogenesis or anomalies of vascularization in the superficial mucosa, which can consequently be biopsied [10]. According to the systematic review and meta-analysis of Di Maio and Spriano et al., this technique can improve diagnosis in up to 35% of the cases (with a pooled sensitivity and specificity of 0.83 and 0.88, respectively), suggesting the site to biopsy [11].

2.2. Imaging and Pathology

Diagnostic ultrasound is performed when a persistent cervical mass is present in the neck. The investigation can distinguish solid from cystic masses, provides details regarding intranodal anatomy, and is very accurate in demonstrating dimension (1 or 2 cm cut-off), shape (roundness index), and ecostructures (destructured germination center or cystic lesion) of the lymph node [12].

Thereafter, it is important to perform ultrasound-guided fine-needle aspiration cytology (FNAC) or fine-needle aspiration core biopsy (FNAB) to make a cytological or histopathological diagnosis of squamous cell carcinoma. US-FNAC is most commonly performed as it is easier to perform and minimally invasive compared to FNAB (core biopsy). The latter procedure is useful to obtain more material for histology instead of just cytology [13].

We have to pay particular attention when a cervical mass is of a cystic nature. US-FNAC, in many cases, may suggest a diagnosis of a second branchial cleft cyst because of poor or non-diagnostic material yield on needle aspiration [14].

Therefore, in adult patients who present with a cystic cervical mass, it is recommended to perform a core biopsy to obtain the right material for proper diagnosis. Moreover, cystic lymph nodes suggest a papilloma virus-induced primary site in the oropharynx.

Excisional biopsy is generally not recommended as it can disseminate cancer along muscle bands of the neck. However, the procedure can be performed in cases whereby US-FNAC or US-FNAB results were non-conclusive. A frozen section analysis is recommended in these cases, and a neck dissection can be performed in the same setting. An alternative option would be definitive radiotherapy after excisional biopsy: in the retrospective analysis by Iganej and Morgan et al., this modality can also provide excellent control of neck disease [15].

The diagnosis of HPV-related squamous cell carcinoma must be considered nowadays in all OPCUP, especially in cases of a large-sized cystic lymph node non-keratinizing basaloid SCC with occasional necrosis. According to current guidelines, p16 immunohistochemistry is a sensitive marker for HPV testing [16].

Additional specific HPV confirmatory testing such as HPV-RNA assessment using E6/E7 mRNA, research of antibodies against E6 and E7, and HPV DNA polymerase chain reaction could be performed in p16 positive specimens because of rare cases of false positives [17].

Imaging after performing the transcervical US must be completed by contrast-enhanced cervical and thoracic CT scan with iodinated contrast or MRI with or without gadolinium contrast. These techniques are considered to have the same sensibility and sensitivity for primary tumor identification in OPCUP (range between 9% and 23%). However, MRI is

better to study the neck. The diagnostic yield increases up to 73% with MRI 3D T1 weighted high-resolution isotropic volume sequences. These tests are easy to perform, reproducible, and widely available. Patients who have undergone a CT or MRI prior to panendoscopy have higher rates of detection of the primary tumor [18].

CT or MRI imaging is able to show the relationship of abnormal nodes to vascular and visceral structures and can reveal further non-palpable and suspicious nodes situated in the parapharyngeal, retropharyngeal, paratracheal, and mediastinal areas. These hidden nodes might suggest a primary site. CT scan and MRI could also detect mucosal surface defects, which can thereafter be biopsied [19].

If a primary lesion is not evident with CT or MRI, 18-fluorodeoxyglucose positron emission tomography (18fdg PET-CT) should be the next diagnostic step. PET-CT is now the reference technique compared to PET alone and gives more value compared to CT-MRI in the detection of the primary tumor [20].

PET-CT detects 30% of primary lesions and 45% when a panendoscopy is also performed. It identifies in 15% of cases of unknown cervical lymph nodes and in 11% of cases of distant metastases (M). However, the rate of false positives is 40% in the palatine tonsils and 20% in the tongue base due to the physiological sensitivity of this tissue for FDG. The sensitivity is up to 79% and specificity up to 70% in the study by Roh, Han, and Deonarine. 18FDG-PET-TC must be performed before endoscopic biopsies to avoid a 20% rate of false positivity [21].

PET-CT identifies palatine tonsil cancer (56%) better than tongue base cancers (25%) [22].

In a meta-analysis conducted by Zhu et al., performing PET-CT prior to endoscopy under general anesthesia allowed diagnosis of the primary site in 44% of cases with a sensitivity of 97% and a specificity of 68% [23].

2.3. Role of Robotic Surgery in Unknown Primary Detection

The identification of the HNCUP is not achievable in over 40% of patients by means of radiological assessment [24]. When a primary tumor is not detected by available diagnostic modalities, treatment options may encompass a large volume of radiation to the neck and to all potential associated primary mucosal sites with or without chemotherapy or to perform a neck dissection with adjuvant chemoradiation [25].

Treatment with radiation is strongly associated with complications such as dysphagia, xerostomia, mucosal atrophy with mycotic infection, and osteoradionecrosis of the jaw. Identification of the primary site may mitigate these risks by minimizing radiotherapy volumes and preserving vital structures such as the salivary glands and mandible [26].

While there is some retrospective evidence in the literature that suggests improved survival with the identification of the primary tumor, other studies reported that finding the primary tumor site did not change the prognosis. However, finding primary cancer does decrease the rate of potential treatment toxicity and complications [27].

In the past, when all previous examinations were found to be negative, the diagnostic work-up of an unknown primary tumor was completed by panendoscopy and multiple blind biopsies. Despite this work-up, many primary tumors have remained undiscovered [1].

Microlaryngoscopy or panendoscopy under general anesthesia with biopsy of suspicious areas, guided by NBI or by PET-CT, MRI, and CT scan, is now the procedure of choice to detect primary cancer. In the meta-analysis conducted by Meccariello et al., the detection rate is at 50%. Additionally, 80–90% of primary tumors are located in the tongue-base tonsils (64%; range 29.2–100%) or palatine tonsils (28.7%; range 13.5–70.8%) [28]; this is likely due to the fact that small primary tumors can be hidden in areas that are difficult to visualize such as palatine and lingual tonsillar crypts [29]. Thereafter, tonsillectomy ipsilateral to the metastatic lymph node coupled with a tongue base biopsy is performed. Deep biopsy of the tonsil is less effective than monolateral or bilateral tonsillectomy [30].

While a palatine tonsillectomy can be performed using more cost-effective traditional approaches, transoral laser microsurgery (TLM) and transoral robotic surgery (TORS) are

the most recent modalities used to detect or treat primary tumors localized in the tongue base in OPCUP [31,32].

The TORS procedure has obtained a rate of primary tumor detection from 70% to 90%. It allows safe and precise removal of the entire tongue base mucosa bilaterally and lingual tonsils, from the midline to the lateral pharyngeal wall and from the circumvallate papillae to the vallecula, using the muscular layer as the deep plane of dissection [33].

The retrospective study of Patel et al. reported rare adverse events from the procedure, including hemorrhage in 5% of patients, the need for tracheostomy in 3% of cases, gastrostomy tube in 3% of patients, and tongue swelling in 1% of patients [34].

The problem of the contralateral tumor to metastatic lymph node or bilateral synchronous primary tumor is under discussion. According to retrospective studies by Koch et al. and Kothari et al., the primary tumor was found in 6% of cases in the contralateral tongue base in 15% of cases in the contralateral tonsil. These data support the use of bilateral tonsillectomy for both palatine and lingual tonsils [35,36].

3. Discussion—Summary

Given the lack of prospective randomized trials, the detection, work-up, and management of HNCUP remains highly variable. A significant proportion of primary tumors is still undetectable even though detailed physical examination with fiberoptic nasopharyngolaryngoscopy and high-resolution imaging are widely available.

Positron emission tomography associated with computerized tomography (PET/CT) scanning allows to detect the occult cervical lymphatic disease and to detect the site of unknown PT and distant metastases. A recent meta-analysis [7] of 246 patients reported an overall sensitivity of 97% and specificity of 68%. Functional and molecular information can also be achieved using magnetic resonance imaging (MRI), as diffusion-weighted MRI (DW-MRI) characterizes tissues in relation to the differences in tissue water mobility. Wang et al. [8] reported 86% accuracy, 84% sensitivity, and 91% specificity of DW-MRI in the prediction of malignancy. Furthermore, integrated PET/MRI scanners have been successfully applied to oncologic imaging within the last few years, demonstrating a better quality in the identification of cervical metastasis in comparison with PET/CT [9,12].

Recently, the introduction of trans-oral robotic surgery (TORS) has introduced a new role of surgery in the primary tumor detection and subsequent management of patients with HNCUP, considering that the most common locations of HNCUP are at the oropharyngeal sites, especially given the rise in the incidence of HPV positive SCC. Consequently, radiation therapy may be delivered to a more defined volume of tissue instead of total mucosal irradiation, decreasing post-radiation morbidity (dysphagia and xerostomia) related to wide and unnecessary radiation to sensitive, normal structures, such as the pharyngeal constrictors and salivary glands [13] (see Figure 1).

Finally, many research studies are focused on demonstrating that OPCUP HPV-positive can be subject to a de-intensification treatment to decrease toxicity, maintain the prognosis, and improve the quality of life.

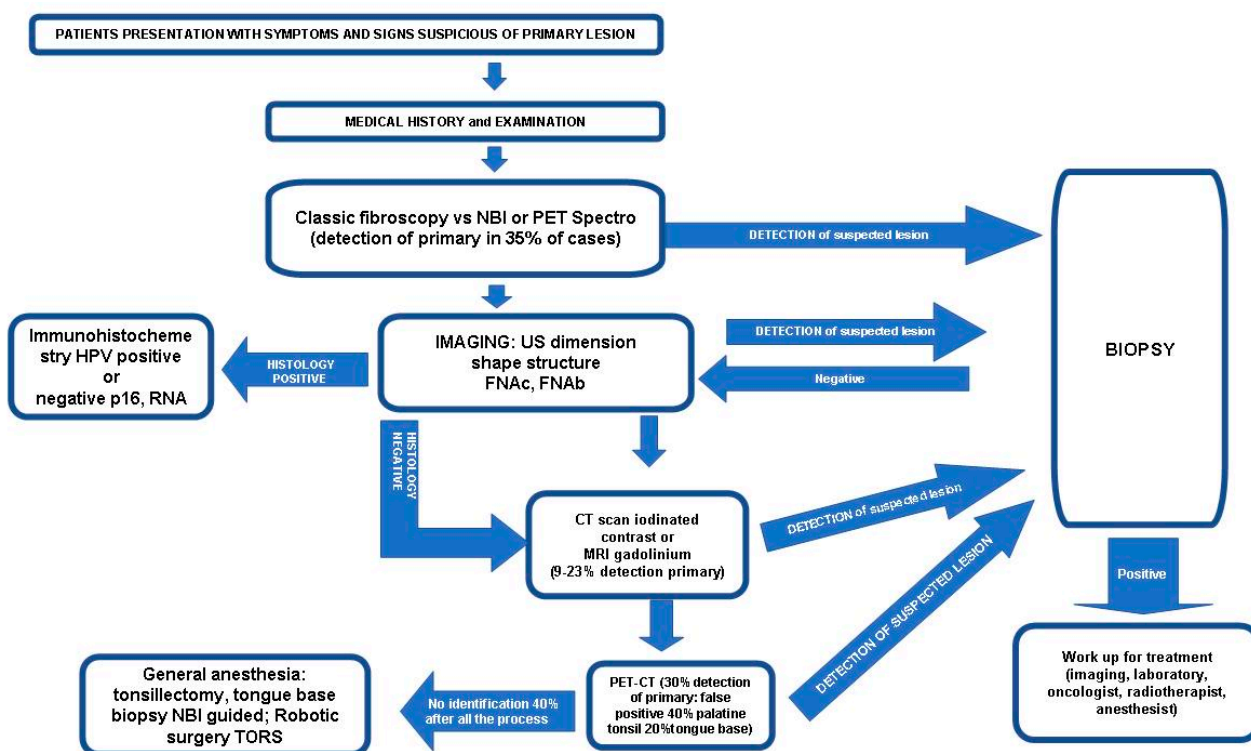


Figure 1. Oropharyngeal primary unknown cancer diagnostic work-up flow chart.

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