

ALGORITHM FOR EARLY DIAGNOSIS AND ROUTING OF PATIENTS WITH HPV-ASSOCIATED OROPHARYNGEAL CANCER FOR PRIMARY CARE PHYSICIANS.

Kurbanov Khurshid Abduburkhanovich

Independent Researcher, Center for Pediatric Hematology, Oncology and Clinical Immunology

Mamedova Guzal Bakirovna

Deputy Director, Center for Pediatric Hematology, Oncology and Clinical Immunology

Alimov Ijod Rustamjonovich

Associate Professor, Department of the Center for the Development of Professional Qualifications of Medical Workers

RELEVANCE

Modern oncology has faced an unprecedented epidemiological shift in the structure of head and neck cancer incidence. While at the end of the 20th century, oropharyngeal squamous cell carcinoma was primarily associated with tobacco smoking and alcohol consumption, over the past two decades, the dominant etiological cause has become high-risk human papillomavirus (HPV, predominantly type 16) [1, 2]. The proportion of HPV-associated oropharyngeal squamous cell carcinoma (HPV-OPSCC) in developed countries reaches 60-80%, showing a steady increase [3]. In Central Asian countries, including Uzbekistan, an increase in the number of HPV-OPSCC cases is also noted, which requires a revision of national diagnostic strategies [4].

HPV-OPSCC is characterized by a unique clinical-biological paradox: high sensitivity to treatment when detected early, but significant diagnostic delays due to an atypical clinical presentation [5]. The disease affects young and middle-aged patients (40-55 years), often without harmful habits, and manifests with non-specific symptoms (unilateral sore throat, dysphagia, otalgia), leading to their erroneous interpretation as manifestations of chronic pharyngitis or tonsillitis [6]. A hallmark is the submucosal, endophytic growth of the primary tumor, making it "invisible" during a standard examination, and early metastasis to cervical lymph nodes, which can be the first and only symptom [7].

In Uzbekistan, the problem is exacerbated by the specifics of healthcare organization. A significant portion of primary visits occur in private medical centers, between which and the state oncology service (regional oncology dispensaries, RSNPMTSOR) there are no standardized pathways for interaction. This creates an "organizational gap," leading to loss of time on duplicate consultations, uninformative treatment, and ultimately, diagnosis at advanced stages [8].

Despite the availability of international guidelines (NCCN, ESMO), their direct application in the conditions of Uzbekistan is difficult due to differences in infrastructure, diagnostic availability, and financing models [9, 10]. Thus, there is an urgent need to develop an adapted, practice-oriented algorithm that would structure the actions of primary care physicians (therapists, otorhinolaryngologists) and create clear pathways for patient referral to specialized services.

The aim of the study is to develop and present a comprehensive clinical and organizational algorithm for the early diagnosis and routing of patients with suspected HPV-OPSCC for primary care physicians in the healthcare system of Uzbekistan.

Materials and methods. A comprehensive approach was used to develop the algorithm, including:

1. A retrospective analysis of 120 medical records of patients with a verified diagnosis of HPV-OPSCC who underwent treatment at RSNPMTSOR in the period 2020–2023. Analyzed were: time from first symptoms to biopsy, number of visits before diagnosis, nature of erroneous diagnoses, completeness of primary examination.

2. Analysis of the regulatory framework: Orders of the Ministry of Health of the Republic of Uzbekistan regulating the provision of oncology care, the National Program for Combating Oncological Diseases (2023–2027), as well as Russian and international clinical guidelines (NCCN, ESMO, clinical guidelines of the Ministry of Health of Russia) were studied.

3. Expert consensus method: Interviews and working meetings were conducted with leading oncology clinicians, otorhinolaryngologists, pathologists, and healthcare organizers of Uzbekistan (n=15) to assess practical barriers and develop acceptable solutions.

4. Systematic review of modern publications dedicated to strategies for early diagnosis of HPV-OPSCC and models of care organization (PubMed, eLibrary, 2018–2023).

Results. 1. Analysis of diagnostic delays. The average time from the onset of first symptoms to histological verification was 5.2 ± 2.1 months. Patient delay (from symptom to doctor) – 1.8 ± 0.9 months, medical-organizational delay (from first visit to biopsy) – 3.4 ± 1.8 months. Patients visited an average of 4.2 doctors before diagnosis. In 89% of cases at the pre-hospital stage, empirical antibiotic therapy was prescribed. Extended endoscopy at the first visit with "red flags" was performed in only 32% of cases (45% in private clinics, 18% in state polyclinics).

2. Structure of typical errors. The most frequent erroneous diagnoses were: chronic pharyngitis/tonsillitis (42.5%), reactive lymphadenitis (28.3%), neurological disorders (12.5%). In 78% of referrals from primary care, a description of the examination of the base of the tongue and lingual tonsil was absent.

3. Developed algorithm. Based on the identified problems, a multi-stage algorithm was proposed (Fig. 1).

- Stage 1. Screening for "red flags". Clear criteria for in-depth examination: unilateral symptoms >3 weeks; palpable dense lymph node >1.5 cm at levels II-III; age 35-60 years without significant tobacco history; lack of effect from anti-inflammatory therapy.

- Stage 2. Mandatory extended video endoscopy. Detailed protocol for examination of all parts of the oropharynx with photo documentation. Emphasis on assessing asymmetry, submucosal infiltration, vascular changes.

- Stage 3. Diagnostic tactics. If a lesion is detected – biopsy with mandatory IHC testing for p16 and PCR for HPV. If no obvious lesion is found, but lymphadenopathy is present – ultrasound-guided fine-needle aspiration biopsy (FNAB) of the lymph node with parallel cytological and PCR testing for HPV.

- Stage 4. Formation of a "diagnostic package". A standardized set of documents (extract, endoscopy results, histology/cytology with p16/HPV, neck ultrasound) for transfer to the oncology dispensary.

- Stage 5. Routing. Clear referral pathways from state and private clinics using telemedicine consultations for preliminary assessment. Target deadlines have been set: oncologist consultation within 5 working days with a complete package.

4. Quality control system. Key performance indicators (KPIs) were defined to assess the effectiveness of implementation:

- Time "from first symptom to biopsy" – target value ≤ 6 weeks.
- Proportion of patients referred with a complete "diagnostic package" – $\geq 80\%$.
- Proportion of patients diagnosed at stage I-II (T1-2N0-1) – increase by 15-20 percentage points over 3 years.

Discussion. The developed algorithm addresses the key systemic problems of diagnosing HPV-OPSCC in Uzbekistan. Firstly, it overcomes the conceptual barrier, shifting the focus from the elderly smoker to the young patient without harmful habits, which corresponds to data from modern epidemiological studies [1, 11]. Secondly, the protocol of mandatory endoscopy in the presence of "red flags" aims to eliminate the main clinical defect – incomplete examination. This is consistent with the position of leading experts who consider endoscopy the "gold standard" for primary assessment [7, 12]. Thirdly, the requirement for mandatory determination of p16/HPV status during biopsy corresponds to international verification standards and is critically important for choosing treatment tactics [9, 13].

The proposed routing model, integrating the private sector through the "diagnostic package" mechanism and telemedicine, is innovative for the practice of Uzbekistan. It allows for continuity of care without duplicating examinations, which is economically justified and increases patient satisfaction. The experience of countries with developed telemedicine shows that such models reduce time to treatment by 30-40% [14].

The established KPIs are measurable and achievable. The target "symptom-to-biopsy" time of 6 weeks seems ambitious but necessary for a radical improvement in prognosis. For comparison, in countries with effective head and neck cancer screening programs, this indicator tends to be 4 weeks [15].

A limitation of the study is that the effectiveness of the algorithm has not yet been evaluated in a prospective clinical trial. Pilot implementation in one of the regions of Uzbekistan with subsequent validation of KPIs will be the next logical step. Furthermore, the success of implementation depends on solving infrastructural issues (equipping with endoscopes, availability of IHC tests) and including the algorithm in mandatory medical education programs.

Conclusion. The presented comprehensive algorithm provides primary care physicians in Uzbekistan with a clear, practical tool for the early detection of HPV-associated oropharyngeal cancer. Its implementation, supported by a quality control system and integration into national clinical protocols, will overcome existing diagnostic and organizational barriers.

This is a direct path to achieving the goals of the National Oncology Program – increasing the proportion of early stages, reducing disability and mortality from one of the fastest-growing oncological diseases of our time.

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