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MODERN TREATMENT AND PREVENTION OF OROPHARYNGEAL CANCER

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ABSTRACT

Squamous cell carcinoma of the head and neck organs ranks 5th in the structure of cancer incidence in the world. Mortality from this pathology has not changed for several decades, despite significant successes and achievements in modern clinical oncology. The article considers and analyzes in detail: the etiological role of human papillomavirus (HPV) in the development of oropharyngeal cancer; sexual and age-related features of HPV-associated cancer, various methods of predicate diagnosis, specific prevention. Conclusions are drawn: papillomavirus infection is the main cause of a sharp and continuing increase in the incidence of oropharyngeal cancer, mainly among men in many countries of the world; vaccination carries positive expectations in the prevention of oropharyngeal cancer.

Introduction.

For the first time, information appeared about a clear tendency to a sharp increase in survival in patients with oropharyngeal cancer.

Interestingly, the trend was observed mainly in male patients under 60 years of age and was not observed in the older age group [1]. The efforts of a series of discoveries that radically changed the vector of development of clinical thought in this branch of oncology. Almost immediately, during the 90s of the last century, works began to accumulate indicating a possible etiological role in the development of oropharyngeal cancer of the human papillomavirus (HPV), namely the most dangerous types of HPV in terms of carcinogenicity [2]. By that time, it had already been proven, thanks to the work of the future Nobel laureate Professor H. According to Harald zur Hausen, HPV is etiologically associated with the development of cervical cancer, but such a connection with such a localization as oropharyngeal cancer did not seem so obvious in connection with sexually oriented transmission.

Epidemiology and vaccination of this type of virus [3]. The final answer was presented in the publication ML Gillison, published in 2000 in the journal of the National Cancer Institute of the USA. The article proved the presence of viral DNA in the nuclei of tumor cells and revealed the genetic and morphological features of this type of cancer. At the same time, it became clear that, despite the common morphological affiliation, this "new" type of oropharyngeal cancer is often not associated with the main etiological factors of the development of squamous cell carcinoma in the head and neck, namely tobacco and alcohol [4]. In 2005 WHO has included HPV in the list of etiological factors for the development of oropharyngeal cancer [5]. A retrospective analysis of epidemiological data accumulated in the United States from the late 1980s to the mid-2000s, presented in A. Chaturvedi showed a clear trend towards a decrease in the incidence of oropharyngeal cancer etiologically associated with alcohol and tobacco, and an increase in the incidence of HPV-associated cancer. At the same time, the proportion of HPV-associated cancer increased from 16 to 73% of the total number of cases of pharyngeal cancer. Interestingly, the overall incidence of oropharyngeal cancer changed slightly over the same time period. By 2030, the expected incidence of oropharyngeal cancer in the United States will increase so much that this pathology will account for almost half of all head and neck cancers, and by 2020 The number of cases of HPV-associated oropharyngeal cancer will be higher than the number of new cases of cervical cancer [6].

Experimental part

Oropharyngeal cancer (CDC US) is one of only five types of cancer, the incidence of which has continued to increase and will continue to increase for another 30 years [7]. 600 thousand new cases of head and neck cancers are registered annually in the world, 37 thousand of them are associated with HPV. The vast majority (78%) of these tumors are oropharyngeal cancer, with a much smaller number of oral and laryngeal cancers, which account for only 2% of the total number of cases each in their own group. Such a distribution has a rational explanation. As is known, in order to realize its potential, the human papillomavirus needs to reach the basal layer of the epithelium, where it penetrates into the cell and begins replication.

In the area of the upper respiratory and digestive tracts, there are lacunae of the palatine and lingual tonsils, in the depth of which there are natural interruptions of the lymphoreticular epithelium and the access of the virus to the basal layer has no obstacles in the form of a multilayer flat epithelium [2]. In this regard, special attention should be paid to the study of the effect of refusal to perform therapeutic tonsillectomies on the increase in the incidence of HPV-associated oropharyngeal cancer [8]. At the same time, according to a population analysis conducted in Denmark, the risk of developing cancer in the area of the palatine tonsils decreases by almost 60% in a group of people.

Interestingly, HPV-associated oropharyngeal cancer is more common in men than in women (5:1). This fact is best studied in a population-based study conducted in the United States. Thus, from 2000 to 2009, the incidence of oropharyngeal cancer in the United States increased 4-

fold in the male population compared with the female [10.20]. This, in turn, is explained by the more frequent spread of carrier in the oropharyngeal region in the male population of dangerous HPV types 16 and 18. If we talk about the overall picture, 85% of HPV-associated head and neck cancers are associated with 16 and 18 types of the virus, and type 16 accounts for almost 95% of these cases [20].

Features of sexual behavior are the strongest risk factor for oropharyngeal cancer. According to one of the national surveys conducted in the United States, from 2009 to 2012, the main risk factors for infection with dangerous types of HPV are the number of sexual partners who practice oral sex throughout their lives. The risk and frequency of infection increase with an increase in the number of partners, and in the male population this indicator continues to increase throughout life up to 15 partners (3 times more than in the female population). What is even more remarkable is that men are infected much more often from women than vice versa [11]. It should be noted that such a pronounced sexual difference in the frequency of HPV infection cannot be explained only by the peculiarities of sexual behavior.

Researchers call the weakly expressed and short the duration of the immune response after the development of primary genital infection in men, and, as a result, a decrease in protection against re–infection during oral contact. In contrast, a significantly high level of immune response in females under the most normal conditions reduces the risk of re-infection with dangerous HPV type 16 by 50% [12]. Interestingly, there are two peaks of infection with dangerous types of HPV through oral contact in the male population. which fall on the age group of 25-30 and 55-60 years [7, 13].

At the same time, the median development of HPV-associated oropharyngeal cancer is 58 years [6]. Thus, it is not difficult to calculate that the latent period of development of HPV-associated oropharyngeal cancer is approximately 10-30 years [7]. The effectiveness of primary prevention using HPV vaccines is 90-100% in terms of preventing HPV infection, which is expected to lead to a sharp global decrease in the incidence of cervical cancer by 2050 [14]. At the same time, the question of the effectiveness of vaccination against HPV infection through oral contact and related diseases remains open.

Clinically significant endpoints, for example, a decrease in the frequency of precancerous pathology, however, such an assessment and clinical studies are impossible for HPV-associated oropharyngeal cancer, since there are no such precancerous conditions in this nosology. In 2014 WHO recommended that regulatory authorities also take as such an assessment indicators for reducing the incidence of HPV infection and carriage as an acceptable endpoint [15]. Thus, in one study, a decrease in HPV infection by oral contact was noted in the female population when evaluated 4 years after vaccination compared with the placebo group [16]. However, with the obvious success of such prevention, it is impossible to expect a decrease in the incidence of oropharyngeal cancer in the future earlier than it will happen for cervical cancer, given the later age of the median development of HPV-associated oropharyngeal cancer. In this regard, we should not expect a change in the current trend in the incidence of oropharyngeal cancer after widespread vaccination before [7].

The prevention of HPV-associated oropharyngeal cancer in the population of HPV carriers also raises the question of the current lack of reliable diagnostic methods for determining precancerous conditions and early forms of cancer of this localization. Identification of HPV infection markers can be useful in identifying high-risk groups. Thus, in some studies it has been shown that the presence of HPV infection in the oral cavity (in general or specifically type 16) or an increased level of antibodies to viral particles in plasma (L1, E6, E7) is associated with a high risk of developing oropharyngeal cancer [17]. This correlation is partly explained by the low prevalence of HPV type 16 carriers in the oropharynx (about 1%) and antibodies to HPV type 16 particles in blood plasma (0.5–5%) in the population of healthy people. The prognostic significance of diagnostic techniques lies in the identification of high-risk groups and is determined by the sensitivity of the techniques. However, at present, low sensitivity does not allow them to be used as accurate diagnostic tests [17.18]. In one recent study, it was shown that the

presence of antibodies in the blood to HPV type 16 E6 over a long period of time (more than 10 years) It can be a predictor of the development of oropharyngeal cancer, thus making it possible to determine an increased risk group [19].

The results of these methods, the rarity of markers and the low incidence of HPV-associated cancer in the general population make its screening an extremely difficult task. Approximate calculations demonstrate the following indicators. In the United States, 1.3% of men and women aged 40-69 years (1.4 million people) are carriers of HPV type 16 in the oropharynx. Approximately 0.7% of carriers of HPV type 16 have an associated cancer in the oropharynx in the future. As a result, 10,500 people need to be screened to identify one case of HPV-associated cancer [7]. It becomes clear what huge resources need to be attracted to conduct effective screening in this risk group. An equally important issue is the influence of a new etiological factor on the clinical course of the tumor process.

HPV-associated oropharyngeal cancer has a significantly better prognosis compared to another type of cancer that is caused by alcohol and tobacco. In most cases, HPV-associated oropharyngeal cancer is diagnosed in young people who do not smoke or have quit smoking for a long time, who do not abuse alcohol. It should be noted that smoking in itself is an independent unfavorable prognostic factor that significantly worsens the prognosis of the disease even in the HPV-associated cancer group.

Results

Treatment of patients in the oropharyngeal cancer group. As a result, the authors identified 3 groups of patients depending on the combination of the most significant risk factors for patient survival. Thus, the low-risk group for disease progression with the highest overall 3-year survival rate (93%) consisted of patients with HPV-associated oropharyngeal cancer, non-smokers or early smokers, with small metastases in the area of regional lymph nodes in the neck. The group at high risk of progression with the lowest survival rate (46%) consisted of patients with HPV-negative oropharyngeal cancer, with smoking experience of more than 10 years, with the maximum size of the primary tumor (T4 according to the TNM system).

The study identified a group with an intermediate risk of disease progression – patients with HPV-associated cancer, smokers, with pronounced metastases in the area of regional lymph nodes in the neck. In this group, the positive effect of having an association of cancer with the HPV virus was largely offset by smoking, leading to a marked decrease in 3-year survival (71%) [25]. And yet, more often the primary tumor in the HPV-associated cancer group is represented by a tumor of small or even microscopic size (visually undetectable), combined with large metastases in the regional lymph nodes in the neck. In accordance with the previous classification of malignant tumors (TNM 7), most of these cases fell into the group with stage IV of the tumor process precisely because of the pronounced tumor process in the neck. At the same time, long-term results after the end of treatment in the group of HPV–associated cancer of advanced stages (III-IV stages) are very high, with a 3-year survival rate exceeding 80% [21, 22]. It turns out that the prognosis in this group of patients is disproportionately better in comparison with early-stage tumors in the group of HPV-unassociated oropharyngeal cancer [17]. A number of studies have shown that the risk of death in the HPV-associated cancer group is reduced by 60-80%, which in itself is a huge statistical difference in clinical oncology [6, 24].

Changes in the new 8th edition of the international classification of malignant tumors (TNM 8), where for HPV-associated oropharyngeal cancer, a tumor process of any size and spread does not involve entering stage IV, except for the presence of distant metastases. An interesting proposal, in the new edition of TNM, is to choose a method for determining membership in the group of HPV-associated oropharyngeal cancer by detecting a specific protein p16 in the tumor (IHC reaction). There is still debate about the objectivity of classifying a tumor as an HPV-associated cancer group based on a particular method for determining the virus in a tumor, due to the fact that there are a certain number of erroneous results.

Methods for determining the human papillomavirus in a tumor include PCR diagnostics, however, it should be noted that this method has a high percentage of false positive results, due to the

possibility of another type of virus, unrelated to the development of cancer, entering the test sample. Thus, a clinically significant technique for determining HPV-associated cancer is one that allows the detection of a transcriptionally active variant of the virus. There are several similar methods – in-situ hybridization, or ISH reaction, real-time PCR with the determination of mRNA of viral oncoproteins E6 and E7 and DNA sequencing.

Integrate them widely into clinical research. The only alternative to these methods, which has all the necessary advantages (cheapness, speed of execution, readiness for use), is the determination of the p16 protein in the tumor using immunohistochemical analysis (mouse antibodies), which also reflects the transcriptional activity of the virus in the tumor.

HPV, the concentration of which increases in the tumor itself in response to the blocking of the function of the retinoblastoma gene protein (RB1) by viral oncoprotein E7. Due to the fact that in HPV-associated oropharyngeal cancer, a similar situation is observed in all cases, this test turns out to be true-positive almost always. To date, many studies have proven a high correlation of this method with the prognosis of the disease in HPV-associated oropharyngeal cancer, regardless of the treatment option [25]. However, it must be remembered that the loss of the RB1 gene, accompanied by increased expression of p16, can also occur in HPV-negative cancer (in 5-8% of cases) due to sporadic mutations in the tumor. Therefore, unlike oropharyngeal cancer, this test is not applicable to squamous cell carcinoma of other localities in the head and neck, in which the frequency of association with HPV is low [17].

There is evidence that nasopharyngeal cancer can be associated with two types of viruses – Epstein-Barr and HPV. It is well known that Epstein-Barr virus is an etiological factor of nasopharyngeal cancer, especially its undifferentiated variant, however, this type of virus is not always detected in patients. So in the work of M. H. Stenmark et al. The data shows that in 30% of patients included in the nasopharyngeal cancer study, the Epstein-Barr virus was not detected, the cancer was associated only with HPV. In addition, another 28% of patients had no association with any type of virus at all, but smoked and/or consumed alcohol [17]. It is important to note that nasopharyngeal cancer associated with HPV had a worse prognosis in terms of survival than that associated with Epstein-Barr virus. It should also be noted that the worst prognosis (the total 5-year survival rate did not exceed 18% compared to 72% for Epstein-Barr virus associated cancer) was observed in the nasopharyngeal cancer group not associated with any virus, which is most likely caused by a large mutational load of the tumor that arose against the background of prolonged tobacco provocation and alcohol [17]. Interestingly, both oral and HPV-associated nasopharyngeal cancer have a worse prognosis compared to oropharyngeal cancer. Most likely, the cause of this is the tumor environment, in particular lymphocytes infiltrating the tumor.

Conclusion.

Papillomavirus infection is the main cause of a sharp and continuing increase in the incidence of oropharyngeal cancer, mainly among men in many countries of the world. Given that this growth continues to gain momentum, experts are raising the question whether this could be the beginning of an epidemic. Given that the exact etiological factor in the development of this type of cancer has been discovered, the question arises of the unique possibility of preventing this disease. Vaccination has positive expectations in the direction of reducing the incidence of oropharyngeal cancer, but the first results will not be received until 2060. At least, the first data on the evaluation of the effectiveness of HPV vaccines in relation to the frequency of genital infection in the female population have already demonstrated significant success. It is important to note that in addition to its epidemiological significance, the HPV factor as an etiological factor in the development of head and neck cancer carries a potential key to understanding many issues in the development and treatment of this formidable pathology.

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