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TREATMENT METHOD FOR HPV POSITIVE OROPHARYNGEAL CANCER

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ABSTRACT. This review presents data on the treatment of oropharyngeal cancer associated with human papillomavirus. Human papillomavirus (HPV) is a DNA-containing virus that infects skin and mucous membrane epithelial cells, which can lead to their benign and malignant degeneration. It is a sexually transmitted infection that affects more than 90% of sexually active people. To date, more than 100 types of HPV have been identified, including types 16, 18, and others, the association of which with the occurrence of cancer of the mucous membranes of the oral cavity and pharynx has been reliably proven. The article discusses various options for targeted therapy, modern drug treatment regimens, as well as the results of the most significant randomized trials on this issue.

Keywords: oropharyngeal cancer, Human papillomavirus, squamous cell carcinoma, chemoradiotherapy.

СПОСОБ ЛЕЧЕНИЯ ВПЧ- ПОЗИТИВНОГО РАКА РОТОГЛОТКИ

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АННОТАЦИЯ. В данном обзоре представлены данные о способы лечения рака ротоглотки, ассоциированного с вирусом папилломы человека. Вирус папилломы человека (ВПЧ) является ДНК-содержащим вирусом, поражающим клетки эпителия кожи и слизистых оболочек, что может приводить к их доброкачественному и злокачественному перерождению. Это сексуально-трансмиссивная инфекция, которой заражено более 90% людей, живущих половой жизнью. К настоящему времени выявлено более 100 типов ВПЧ, в том числе типы 16, 18 и др., связь которых с возникновением рака слизистых оболочек ротовой полости и глотки достоверно доказана. В статье

рассматриваются различные варианты таргетной терапии, современные схемы лекарственного лечения, а также результаты наиболее значимых рандомизированных исследований, посвященных данной проблеме.

Ключевые слова: Рак ротоглотки, Вирус папилломы человека, плоскоклеточный рак, химиолучевое лечение.

Introduction. Tumors of the oropharynx include neoplasms localized in the area of its posterior and lateral walls, palatine tonsils, base and posterior third of the tongue, and soft palate. The main etiologic factors in the development of this pathology are considered to be smoking, especially in combination with the consumption of strong alcohol, chewing various mixtures, as well as the human papillomavirus (HPV) (mainly its 16th and 18th types) [1]. HPV-associated oropharyngeal cancer is of particular clinical interest. This is due to a better prognosis and the desire to reduce the therapeutic effect in order to improve the quality of life of patients. HPV-associated oropharyngeal cancer predominantly occurs in young patients without bad habits [2]. Despite the low degree of tumor differentiation and the presence of regional metastases in most cases, the survival rates of patients with this pathology are 2 times higher than those of patients with HPV-negative malignant neoplasms in this location [3]. Currently, patients with HPV-positive and HPV-negative cancers are treated with the same treatment strategy, which is characterized by high toxicity, often leading to discontinuation or modification of therapy. Currently, there are various approaches to the treatment of oropharyngeal cancer, both early stages (T1-T2) and locally advanced forms. When choosing the optimal therapy method, the main focus is on preserving the shape and function of the organ and, accordingly, the patient's quality of life [4]. For early-stage oropharyngeal cancer, radiation and surgical treatment (transoral laser or robotic surgery) are possible. For locally advanced malignant neoplasms in this location, various regimens and types of therapy are also used. Due to the better prognosis of HPV-positive tumors compared to HPV-negative malignant neoplasms, the issue of treatment de-escalation is being considered. Taking into account tumor differentiation, one can speak of higher chemo- and radiosensitivity of tumors associated with HPV compared to tumors not associated with this virus, which could change treatment protocols and improve the quality of life of patients without reducing oncological results [5].

Drug therapy. Historically, chemoradiation therapy using cisplatin has occupied a leading position in the treatment of oropharyngeal cancer. However, given the toxicity of this drug, attempts have been made to replace it with cetuximab. In 2019, the results of the phase III RTOG 1016 study [5] were published, which included 987 patients with T1-2 N1-2 and T3-4 N2-3. They were divided into 2 groups: RT (total focal dose (TFD) 70 Gy over 6 weeks with cisplatin administration at a dose of 100 mg / m2 on the 1st and 22nd days) and cetuximab therapy at standard doses. Overall survival (OS) in the cetuximab group was lower than in the cisplatin group (77.9% vs. 84.6%). Moreover, the toxicity rate (grade III–IV) was similar (77.4 and 81.7%, respectively). Also in 2019, similar results of the randomized De-Escalate study, which included 334 patients,

were presented. The two-year survival rate was 89.4% in the cetuximab group and 97.5% in the cisplatin group [5]. The RTOG 1016 study design differed from the De-Escalate design in that cisplatin cycles were administered on days 1, 22, and 43 at a similar dose (with the same RT dose for 7 weeks). Currently, the Phase III TROG 12.01 study (NCT01855451) with a similar design, which included 189 patients, is ongoing. The planned end date is August 2023. Due to the deterioration in patient survival rates when switching from cisplatin to cetuximab, a number of authors attempted not to replace it, but to reduce the dose. Thus, the RTOG 0129 study assessed the results of cisplatin dose reduction. No differences in OS rates were found between high-dose cisplatin (100 mg/m2) every 3 weeks (3 doses simultaneously) with standard fractionation (70 Gy over 7 weeks) and cisplatin at a dose of 100 mg/m2 every 3 weeks (2 doses simultaneously) with accelerated fractionation (72 Gy in 42 fractions over 6 weeks) [6].

Minimally invasive surgery. Survival rates for early-stage cancer using RT range from 68% to 90% and depend on the location of the primary tumor [7,8]. Meanwhile, when transoral resection with cervical lymph node dissection and adjuvant RT are performed, relapse-free survival rates in some patients (up to 60%) reach 83–95% [9,10]. An analysis of published studies on the treatment of early-stage oropharyngeal cancer by G.R. de Almeida et al. demonstrated comparable results for RT and surgery: 2-year OS rates were 84–96% and 82–94%, respectively [10]. These treatment strategies differ only in their side effects. In 2019, the results of the MS1273 study were published, which included 80 patients with HPV-positive oropharyngeal cancer who had an unfavorable prognosis and underwent surgery at stage 1. The patients were divided into 2 groups: intermediate risk (T3N2, without ECR), LT in SOD 30 Gy with weekly docetaxel administration at a dose of 15 mg/m2, and high risk (T3, with ECR), LT in SOD 36 Gy with docetaxel administration at a dose of 15 mg/m2. The two-year locoregional control in groups 1 and 2 amounted to 96.1 and 91.1%, respectively [11]. Given the contradictory data on the lack of prognostic significance of ECR in HPV-positive oropharyngeal cancer, some authors are considering the possibility of de-intensifying treatment of patients with this pathology [12]. Thus, in the ADEPT study (NCT01687413), an attempt was made to randomize patients with HPV-associated oropharyngeal cancer and the presence of ECG into groups of adjuvants chemoradiotherapy at a dose of 60 Gy and LT at a dose of 60 Gy. However, this trial has unfortunately been discontinued.

Conclusion. Based on an analysis of the literature on HPV-positive oropharyngeal cancer, only limited conclusions can be drawn. Despite the favorable prognosis of this pathology compared to malignant neoplasms of the oropharynx not associated with HPV, treatment strategies remain the same. In the case of early-stage cancer, given the equal effectiveness of both radiation therapy and minimally invasive surgery, the choice of treatment strategy remains with the specialist. New treatment strategies involving minimally invasive technologies improve functional outcomes only when used alone. Although phase II trials have yielded promising data regarding deintensification of therapy, it is premature to

draw conclusions until the results of randomized phase III trials are available. The key is to balance treatment effectiveness with patient quality of life.

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