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Comparative Evaluation of The Effectiveness of Systemic and Intra-Arterial Chemotherapy in Patients with Laryngeal Cancer

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ABSTRACT

One of the options for increasing the effectiveness of therapy in patients with head and neck cancer is the use of intra-arterial chemotherapy (IACT), but its use is rather controversial, therefore, in this work, we examined the effectiveness of IACT compared with standard (systemic) polychemotherapy (PCT) in patients with laryngeal cancer. **Methods:** The efficacy and toxicity of IACT and systemic PCT in patients with laryngeal cancer (n = 21, n = 23 respectively) were analyzed. **Results**: The data revealed an increase in the number of patients with tumor regression by more than 50% when using IACT, which showed lower toxicity and better tolerance compared to systemic PCT. **Conclusion**: AICT has great potential for the treatment of patients with laryngeal cancer in the neoadjuvant preoperative period.

INTRODUCTION

Malignant tumors of the head and neck remain an important problem in modern oncology, and cancer of the oral cavity, pharynx, and larynx is the most common in patients with this nosology. An estimated annual incidence of head and neck cancer achieve 700,000 cases, accounting for 4.9% of cancer cases worldwide [*1*]. Alcohol and tobacco abuse are common etiological factors for oral, oropharyngeal, and laryngeal cancer. In addition, Epstein-Barr virus infection correlates with the development of nasopharyngeal cancer, and human papillomavirus (HPV) infection also correlates with the development of oropharyngeal cancer [*2*]. Today, there is no single optimal treatment for such patients, since each case requires an integrated approach and a multidisciplinary consultation [*3*]. The choice of a complex of treatment methods is influenced by a large number of factors, while one of the options for increasing the effectiveness of therapy in patients with this nosology is the use of intra-arterial chemotherapy (IACT), which was first used in the treatment of head and neck tumors in the middle of the last century [4]. Klopp et al. were the first to use IACT: they developed a suitable technique for re-injecting nitrogen mustard through a polyethylene tube inserted through the proximal arterial branch directly into the artery. They administered nitrogen mustard to several patients with head and neck cancer and reported positive results that were not observed with intravenous (IV) administration of the drug. However, the practical application of such a therapeutic approach at that time was limited by the lack of specificity of nitrogen mustard and a seriously destructive effect on normal adjacent structures [*5*].

Laryngopharyngeal cancer is characterized by an aggressive course and diffuse local spread, early regional metastasis, and a relatively high incidence of distant metastases. In about 80–85% of cases, the diagnosis is made at stages III-IV of the disease, when more than 50% of patients have clinically detectable metastases in the cervical lymph nodes, and 17% of patients have distant metastases [*6,7*]. The choice of complex treatment methods is influenced by a large number of factors, while one of the options for increasing the effectiveness of therapy in patients with this nosology is the use of IACT.

Blood supply to head and neck tumors occurs mainly via the branches of the external carotid artery, and relapses are more common in the primary lesion or regional nodes of the neck, while distant spread occurs late and is not such a common cause of morbidity and death [*2*]. Since the

preservation of function and appearance during the treatment of patients with head and neck cancer is a significant factor, the use of IACT in this nosology always remains at the center of attention. At the same time, despite the long experience of using IACT for the treatment of head and neck cancer, it is not widely accepted, since, according to some authors, the overall response rates do not differ significantly from standard therapeutic approaches, and the use of carotid artery catheterization with implantable pumps remains problematic due to the risk of infection and thrombosis [*2*]. Regarding the potential effectiveness of IACT in the treatment of patients with head and neck tumors, along with various questions about the method of administration, drugs, etc. to improve the results of the treatment, in this work, we have evaluated the comparative effectiveness of systemic and intra-arterial (IA) chemotherapy (CT) in patients with laryngeal cancer.

MATERIALS AND METHODS:

Patients who were treated at the Kramatorsk City Oncological Dispensary (since 2020, CNPE "Regional Territorial Medical Association of Kramatorsk", Ministry of Health of Ukraine) were divided into 2 groups:

Group I - 23 patients with laryngeal cancer T2-3N1M0 (histologically - squamous cell carcinoma) who received complex treatment in 2014-2021. Before surgical treatment, 3 courses of systemic chemotherapy were carried out in a neoadjuvant mode, according to the scheme (docetaxel (Docetaxel Ebeve concentrate 10 mg/ml 8 ml (80 mg)) - 75 mg/m^2, cisplatin (Cisplatin Ebeve 0.5 mg/ml concentrate for a solution of 100 ml (50 mg) bottle No. 1) - 75 mg/m^2.

Group II - 21 patients with laryngeal cancer T2-4N1M0 (histologically- squamous cell carcinoma) who received complex treatment in 2018-2021, ie 3 courses of intra-arterial chemotherapy in a neoadjuvant mode before surgery (5-fluorouracil (5-Fluorouracil Ebeve 500 mg, 10 ml vial) - 1500 mg/m^2 (5 days), methotrexate (MethotrexateEbeve 50 mg solution, 5 ml bottle) - 10 mg, cisplatin (Cisplatin Ebeve 0.5 mg/ml concentrate for 100 ml solution, 50 mg per bottle) – 10mg/m^2.

Subsequently, the patients received surgical treatment and then radiotherapy.

The result was assessed using ultrasound, CT, MRI, videoscopic bronchoscopy in the preoperative period. The effect on tumor size was evaluated before and after chemotherapy.

The toxicity grade was assessed using a 5-point system for assessing the toxicity of chemotherapeutic drugs. The primary index analyzed in this study was the efficacy and toxicity of chemotherapy. Evaluation of the effectiveness of treatment was carried out following the WHO recommendations and was carried out after the third course of chemotherapy, the assessment of the toxicity of treatment was carried out according to the WHO and NCIC standards.

All patients were informed about the examination and provided written consent on the use of the clinical material for research purposes. The research program was approved by the Bioethics Commission of the Kramatorsk City Oncological Dispensary of the Ministry of Health of Ukraine.

RESULTS AND DISCUSSION:

To compare IACT and systemic PCT, we took into account 2 facts: the toxicity grade of the therapy and its effectiveness, which was assessed by the duration of the relapse-free period. As a result, it was noted that in the 1st group of 23 patients who received systemic therapy, 17 (73.9%) had the 2nd toxicity grade, and 5 (26.1%) - the 3rd toxicity grade (Fig. 1) Whereas in the 2nd group consisting of 21 patients who received IACT the 1st toxicity grade was observed in all 100% of cases (Fig. 1). At the same time, the patients developed a local tissue reaction in the form of hyperemia of the zone of regional distribution of the chemotherapy drug - 18 (85.7%) cases, as well as itching and rashes - 2 (9.5%) cases. All of the above symptoms resolved on their own or passed against the background of accompanying anti-inflammatory therapy (Dexometasone (KRKA) injection - 2 mg bolus 2 times a day through a catheter, Suprastin (Egis) tabletted - 25 mg orally, once a day, 3 days).

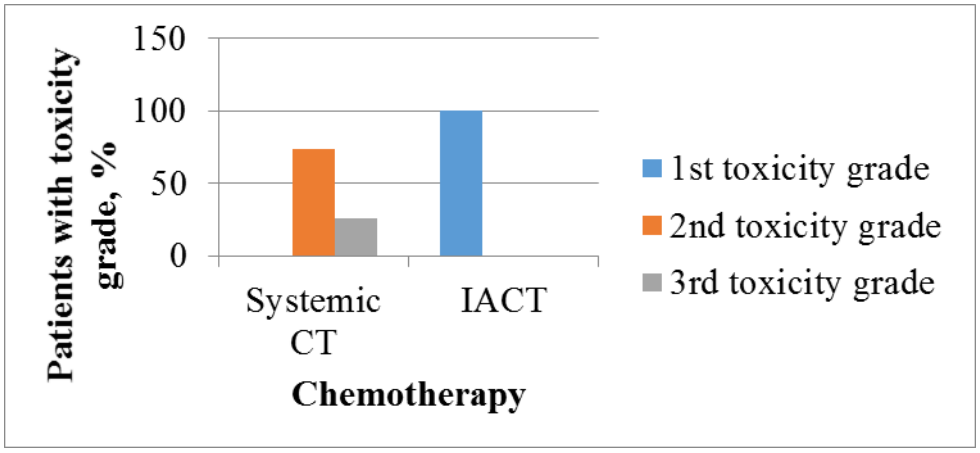

Figure No. 1: The toxicity grade in patients with laryngeal cancer, depending on the type of chemotherapy: systemic or intra-arterial.

When evaluating the effectiveness of the studied treatment variants in patients with laryngeal cancer, the following data on the patterns of the tumor process during the period of three courses of PCT and IACT was obtained, and the result was assessed after 78 days (Fig. 2).

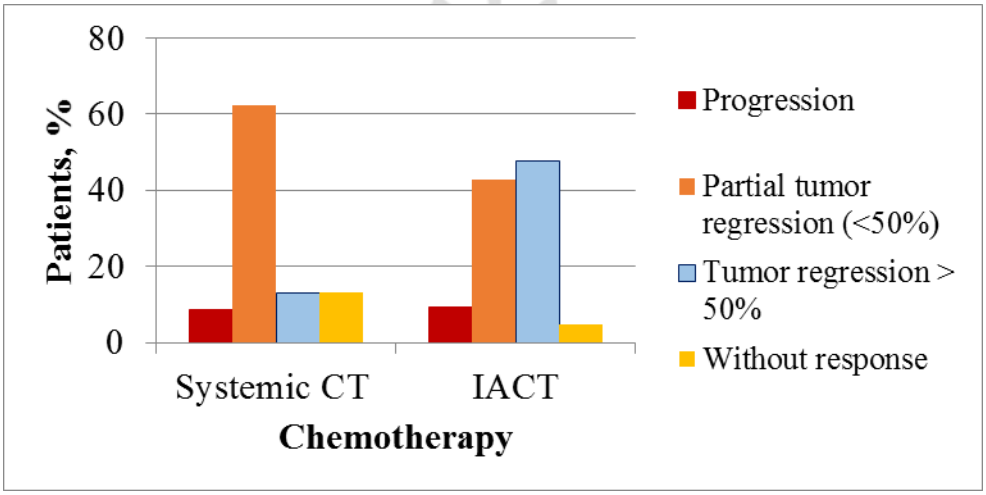

Figure No. 2: The course of the disease in patients with laryngeal cancer, depending on the type of chemotherapy: systemic or intra-arterial.

It was found that in group I, 2 of 23 patients (8.6%) who received systemic chemotherapy showed disease progression, i.e. an increased tumor size and increased number of affected metastatic lymph nodes, in 3 (13.1%) - no changes (no significant dynamics), while in 15

(65.2%) - tumor regression up to 50%, 3 (13.1%) - tumor regression more than 50%, complete tumor regression - 0 (0%).

In group II in 2 of 21 patients who received IACT (9.5%), there was registered a progression of the disease, i.e. an increased tumor size and increased number of affected metastatic lymph nodes (according to our observations, the progression was observed mainly due to the prevalence of the tumor process on the contralateral side larynx), in 1 (4.7%) - no significant dynamics, 9 (42.8%) - tumor regression up to 50%, 10 (47.6%) - tumor regression more than 50%, complete tumor regression - 0 (0%).

Our data allow us to conclude the potential advantage of IACT over systemic chemotherapy due to its lower toxicity and, as a consequence, better tolerance. At the same time, importantly, we obtained a relatively large number of patients with tumor regression > 50% (Fig. 2) when using IACT, which indicates its higher efficiency compared to standard PCT. Also, a high cytostatic effect of the regional distribution zone of the chemotherapy drug was observed, creating a maximum concentration and potentiating the action of the cytostatic.

At the same time, it should be noted that there are some disadvantages of IACT compared to systemic therapy, namely:

- With the use of an infusion pump the duration of chemotherapy is extended for 96 hours.

- Manifestation of local cytotoxic effects of chemotherapy drugs on healthy tissues at the site of their distribution is observed.

In conclusion, our data indicated that IACT has great potential for the treatment of patients with laryngeal cancer in the neoadjuvant preoperative period.

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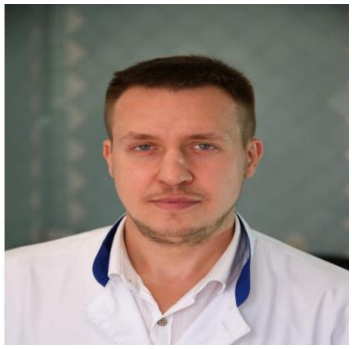

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