

шкової пухлини вирішувалось питання про хірургічне лікування (ларингектомія). В першій групі один рік прожило 87% пацієнтів, три роки - 71,5% хворих, в другій групі - 76% та 51% відповідно.

### Висновки

Поєднання мультифракційною променевої терапії та хіміотерапії може бути самостійним методом лікування РГ та РГГ при II та III стадіях захворювання; Поєднання мультифракційною променевої терапії та хіміотерапії приводить до значно меншого порушення основних показників гомеостазу ніж при застосуванні класичних методик лікування; При хіміотерапії та традиційній ДГТ виявлена більш глибока деструктивна дія на імунотропні клітини, зокрема нейтрофільні гранулоцити, про що інформують дані визначення процесів апоптозу/некрозу останніх, стає очевидним доцільність застосування запропонованої нами схеми хіміотерапії та ДГТ в режимі мультифракціонування; Для прогнозування оптимального вибору методу лікування пацієнтів хворих на рак гортані та гортаноглотки найбільш прогностичне значення мала ступінь експресії Ki-67, p53, bcl-2; Безрецидивний період виживання у пацієнтів, що отримали розроблений нами метод хіміопроменевої терапії був достовірно тривалішим (36±6міс.) в порівнянні з порівнянні з пацієнтами, що лікувались за традиційними методиками (24 ± 4 міс.)

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## ENGLISH VERSION: THE ORGAN SAVE TREATMENT OF THE LOCAL LARYNX CANCER AND HYPOPHARYNX

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*The cancer of the larynx belongs to the group of tumors, which in recent years demonstrates the stability and growing. The incidence in the world reached 500 000 cases per 100 000 population. In Ukraine, for the past 5 years (2001 - 2005) there is the steady increase in the number of ill persons, which is 8% of all cancer pathology. Along with this social importance of this pathology is increasing. So now the problem of organ save treatment since this is the only possible integrated approach. So today it is promising to combine chemotherapy and radiation as a neoadjuvant mode and chemoradiotherapy mode, which allows to reach the larynx preservation in 60% of patients.*

Key words: cancer, larynx, organ save treatment, chemoradiotherapy.

### Introduction

The malignant neoplasm is one of the major health problems in Ukraine and worldwide, the relevance of which is determined by the constant increase -morbidity. According to the WHO 2020 cancer patients come first.

According to recent statistics, the tumor in the maxillofacial area and neck is about 25%. Increase in hypopharynx cancer over the past 10 years was 30.7% in men, women - 17.6%. Cancer localization to date remains the most difficult to diagnose and treat malignant

tumors of the upper respiratory and digestive tracts, which is 1.3% of all malignancies. Neglect in Ukraine for cancer of the larynx and hypopharynx is 57% and 59% of the Poltava region [National Cancer Registry]. The features of cancer of the larynx and hypopharynx are high aggressiveness, rapid infiltrative growth, involving the process of surrounding organs and tissues, high level of regional metastasis - 45-80% [5]. Difficulty of hypopharynx cancer treatment is due to late diagnosis, which in turn is associated with a long latent disease, extensive and early metastasis and variety of clinical manifestations of malignancy. In more than 70% of cases, treatment begins with stage III-IV and approximately 60% of patients diagnosed of regional metastases, and 10% - 20% - bilateral. These stages show combined treatment with performing the laryngectomy with different types of resection hypopharynx, allowing radical removal of the tumor, but inevitably leads to permanent disability due to dysfunction of patients with swallowing, breathing, speech, loss of social adaptation [2,17]. This is the main cause of failure of surgery patients, even when it can be effective. Therefore, the method of choice remains Organ tactics using chemo radiotherapy. The question is the sequence of radiation and chemotherapy, the effectiveness of different chemotherapy regimens, searching for ways to overcome tumor radioresistance and protect healthy tissue.

The purpose of this study is to improve treatment outcomes of patients with cancer of the larynx and

hypopharynx by selecting individually grounded treatment.

**Materials and methods**

To achieve this goal retrospective analysis of 285 case histories of patients with malignant tumors of the larynx treated at the Poltava Regional Clinical Clinic from 2003 to 2007 was made. Among the ill men were 271 (95%), 14 women (5%), completely correlated with the literature value given where the incidence of men and women 1:20. The average age of patients was 56.3 years, that is of working age. The highest incidence noted aged 60 - 69 years old - 94 (32.9%). For patients stages were distributed as follows: Stage I - 17 (5,9%), II stage - 87 (30,6%), III stage - 169 (59,3%), IV stage - 12 (4.2 %). The prevalence of primary tumor is designated by the International classification system of TNM symbols, seventh review and meets T2-3N0-1M0. As to the localization process, in 169 (58.9%) patients we observed lesions larynx, 103 (36.3%) – voice part and in 13 (4.8%) – undervoice part. Morphologically - 99.3% of tumors had the squamous cell carcinoma of the structure. Observations were conducted with 108 patients who, on the basis of a comprehensive integrated entry exam were ascertained the presence of RHH II - III stages and they were divided into groups. Patients were included in the study after receiving information consent for diagnostic and therapeutic manipulations required by study protocol. The criteria for inclusion were patients with cancer of the larynx and hypopharynx T2-3N0-1M0.

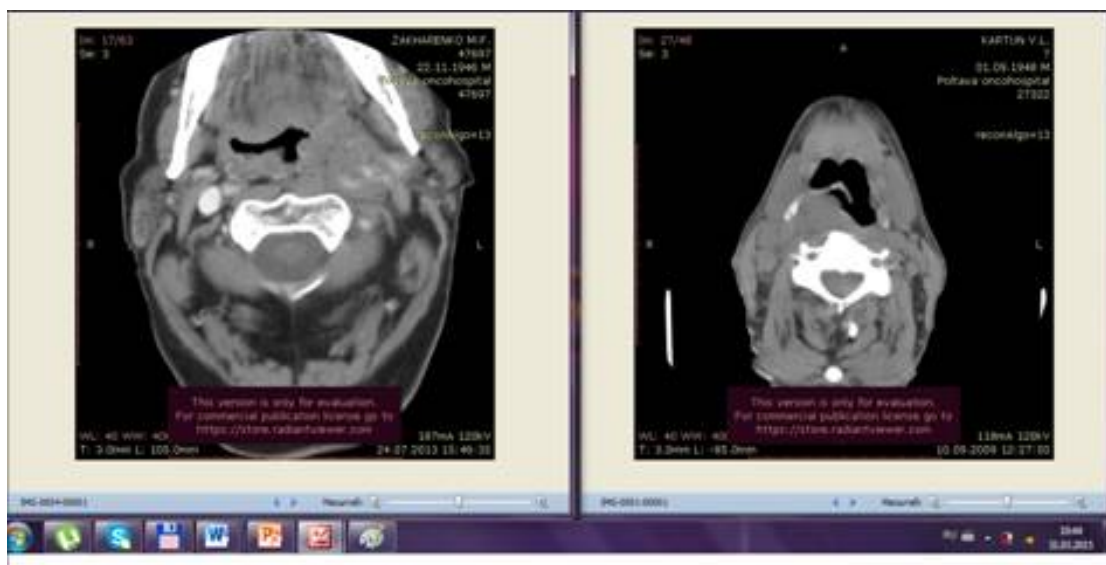


Fig.1. Computed tomography

A comprehensive survey of patients using diagnostic methods was conducted: complete blood count, urinalysis, blood chemistry, ECG, pharyngitis laryngoscopy indirect, direct fibro pharyngitis laryngoscopy, median X-ray tomography, X-ray study of the pharynx, X-ray of OGK, computed tomography (CT) (Fig.1), ultrasound of the digestive tract, morphological methods, immunohistochemical methods, apoptosis of neutrophils.

**Results and discussion**

For comparative evaluation of treatment effectiveness we developed diagnostic and therapeutic approaches tactical versus clinical course and CL and HP II-III. in two

groups of patients. Estimated duration of disease prior to the specialized treatment (after the onset of clinical symptoms of cancer), which is an important factor that influences the outcome.

Remote gamma therapy was performed using the device remote gamma irradiation TERAGAM K-01. Cobalt radiotherapy setting TERAGAM K-01 is designed for radiation therapy of cancer using a beam of gamma radiation. The control system allows for verification of set parameters and modes of exposure, dynamic simulation mode (with the source in working position), the data

printout conducted the session. Calculation of the session is performed using dose-metric system planning.

The first group (56 people)	
I subgroup – comparison (31 person)	II subgroup – research (25 person)
exposure on classic purpose-wild in static mode radiation therapy multifraction daily dose	in static mode.
LED 65 - 70Hr tumor for 35 - 37 fractions (by 2,2Hr). In the first phase of treatment SVD is 40 Gy, then make a break for 3 weeks abatement radiation reactions. If after the first stage of tumor regression than 40 - 50%, DHT continue to LDS 65 - 70Hr.	LED 70 - 74Hr mode Plaines rate in two stages. The daily dose of 2.2 Gy (1,1Hr 2 times a day with an interval of 4 hours). After the first stage of deciding on the effectiveness of treatment or further surgery.
The second group (52 people) chemoradiotherapy	
I subgroup – comparison (27 person)	II subgroup – Research (25 person)
chemotherapy (PCT), cisplatin, 5-FU (two courses repeated at intervals of 3 weeks). Three-weeks irradiation classical-term static method in two stages. chemotherapy (PCT), cisplatin, 5-FU (two courses repeated at intervals of 3 weeks) further exposure mode multifraction i two stages. The first stage is carried out in parallel third year PCTs.	
The first course PCT: 5-FU 170 mg / m2 to 4500-5000 mg. By cisplatin 50 mg / in drops. 1,8,15 day. The second course PCT: 5-FU 170 mg / m2 to 4500-5000 mg. By cisplatin 50 mg / in drops. 1,8,15 day. After a break of three weeks performed irradiation classical method in the static mode, namely LED 65 - 70 Hr. tumor for 35 - 37 fractions by RVD 2,2Hr. In the first phase of treatment SVD hundred-constituted UAH 40gr, then make a break for 3 weeks abatement radiation reactions. If after the first stage of tumor regression than 40 - 50% exposure continues.	The first course PCT: 5-FU 170 mg / m2 to 4500-5000 mg. By cisplatin 50 mg / in drops. 1,8,15 day. The second course PCT: 5-FU 170 mg / m2 to 4500-5000 mg. By cisplatin 50 mg / in drops. 1,8,15 day. After a break of three weeks PCTs (5-FU at a dose of 750 mg / m2 in 1-5 days and cisplatin at a dose of 0.75 mg / m2 1 5 days and simultaneously begin the first phase of a multi-exposure fraction day 2,4Hr dose (1,2Hr 1,2Hr +) with an interval between fractions 4 hours prior to the LED 40gr. 5 g /week. mode split rate.

We studied the expression of radiation reactions in patients treated with radiation therapy using the traditional fractionation and dose at multifraction and signs of intoxication chemotherapy with CRT. We estimated both early and late responses at each of these treatments from the neck skin, mucous pharynx, larynx and oral cavity and blood, hemoglobin, white blood cells, platelets, creatinine, urea, blood enzymes. The Medical pathomorphosis was evaluated by the method V.A Olshansky, E.I Trofimov (1993). Immunohistochemical determination of the level and nature of protein expression can be used as differential diagnostic criteria between severe dysplastic (precancerous) processes and, in fact, crayfish. We determined the proliferative marker Ki activity - 67. This allows determination and proliferation index (PI) studied the proliferative activity of tissues RHH and WG. Epithelial tissue directly matched tumor had signs of hyperplasia and dysplasia. This increased performance expression Ki-67. Thus determining the degree of expression of Ki-67 serves is an important diagnostic, prognostic marker that indicates RHH sensitivity to chemoradiotherapy. Further study was conducted oncoproteins expression of p53, which was associated with the transformation of normal cells into tumor. Using monoclonal antibodies detect p53 oncoproteins expressed mutant. Significant differences in the expression levels of p53 at WP RHH and compared with normal mucosa dysplasia and hypopharynx, show it informative, as an indicator of oncotransformations. The group of proteins that regulate apoptosis, inhibit particular, is oncoproteins bcl-2. It prolongs the life of cells, however expressed, and many tumors. In patients with CL and CH investigated the expression of bcl-2 using monoclonal antibodies and only take into account the specific cytoplasmic staining. The reaction was considered positive for bcl-2 status in the presence of a specific color in 10% or more of tumor cells, in other cases - negative. At low effect of chemoradiotherapy amount of bcl-2-positive 1.6 times higher compared with crayfish with sufficient response to therapy, although these values are not likely.

Bcl-2 positive tumor status may indicate a likelihood of recurrence of the disease within the first year, the low sensitivity of chemoradiotherapy. This suggests its important prognostic markers on prognosis and treatment effectiveness of RHH.

Apoptosis of neutrophils in the case of patients was studied by electrophoresis DNA neutrophils.

For objectification of the results the research was conducted by morphometric recommendations. The results obtained were subjected to statistical analysis using variance results.

Distance - HT patients in both groups underwent satisfactorily. Early radiation reactions were significantly less pronounced in patients of 2nd subgroups. (17.25% vs. 55.6%, p = 0.005). The degree of reaction of the mucous membrane of the larynx and pharynx patients was significantly different. The degree of reaction 4. And subgroups - 40.7% (independent DHT). This shows that the damaging effect is more pronounced when using traditional DPT. The main effect of DPT in both groups is that patients could recognize the cancer process stabilization, which was noted in 44.6%. At the same time, in 26.8% of the cases partial regression of the tumor occurred.

To predict the efficacy of radiation therapy we introduced artificial integrated index of the effectiveness of radiation therapy, which is a prognostic criterion that is formed with a certain amount of points corresponding to the studied parameters. Indicators that we take into account are provided in the table. So we got integral indicator of the effectiveness of radiation therapy in patients with WG and PRHH. To study the effect of a particular type of CRT in patients with hypopharynx cancer we studied the apoptosis of circulating neutrophils. It should be noted that the most characteristic morphological changes in apoptosis are: aggregation of chromatin condensation nuclei and cytoplasm and nucleus and cytoplasm fragmentation and the presence of plasma membrane vesicles coated containing nuclear material fused mitochondria and ribosomes. In analyzing hemogram patients to CRT in patients 1 and 2 subgroups with RHH

after CRT, the presence of varying degrees of degenerative changes in neutrophil granulocytes. The level of spontaneous apoptosis of neutrophils in smears prepared immediately after the taking of blood in patients of 1 subgroup undergoing chemotherapy combined with traditional DHT increased 1.4 times as compared with that of patients for CRT. Thus, blood smears of patients of the main group 1 (comparative) were more common for subgroup of neutrophils morphological features characteristic of cells exposed to apoptotic changes.

To confirm the data obtained in the pre-morphological research shows, performed molecular genetic processes determine the presence of spontaneous apoptosis of peripheral blood neutrophils, namely DNA electrophoresis. Exploring the link between the effect of chemoradiotherapy and consistent use of the proposed methods separately revealed that the combination of the two agents exceeded the effect each of them separately. Concomitant use of these treatments has an advantage due to synergy. The effectiveness of chemoradiation treatments, prognosis by determining the level of expression of Ki-67, p53, bcl-2, the definition IEHPT (index efficacy of chemoradiotherapy), and setting the optimal method of therapy based on statistical analysis, it became clear that 78% of patients WG and RHH (T2-3N0-1M0) may be predictably good results of treatment.

### The results

The analysis showed that the amount of remedial measures is determined depending on the stage of the disease. With the prevalence of T2N0M0 patients received combination therapy, radical surgery followed by radiation and by the classical method of preoperative radiation followed by surgery (with residual tumors). In the treatment of locally disseminated cancer of the larynx T3N0-1M0 used therapeutic method different sequence of radiation, chemotherapy (XT) and surgical components. With the prevalence of patients received palliative T4N0-1M0 chemoradiotherapy. The analysis has been taken into account in 149 (52.3%) patients with T3N0M0, which were distributed into two groups. 78 patients of the first group underwent radiation therapy (December 5 to 2 times a week to 40 Gy) and chemotherapy using platinum drugs, 5-FU and bleomycin. The second group (71 patients) received radiation therapy by the classical method of treatment (2 December 5 times a week to 40 Hr). After the PA and XT in case of residual tumor was a question of surgical treatment (larynxectomy). In the first group 87% survived of patients one year three years - 71.5% of patients in the second group - 76% and 51%.

The combination of multifraction radiation therapy and chemotherapy may be an independent method of treatment and CL and CH at the stages II and III. The combination of radiotherapy and multifraction chemotherapy leads to much smaller violations of basic indicators of homeostasis than with classical methods of treatment; When chemotherapy and traditional DHT we found deeper destructive effects on immunocompetent cells, in particular neutrophilic granulocytes, which informs that apoptosis / necrosis past is feasible to our proposed chemotherapy and DHT mode multifraction. To predict the optimal choice of treatment of patients with cancer of the larynx and hypopharynx most predictive value had the degree of expression of Ki-67, p53, bcl-2; Disease-free survival period in patients who have received chemoradiotherapy method was significantly longer (36

± 6 months) Compared with compared with patients treated by conventional methods (24 ± 4 months).

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