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# Therapeutic effect in patients with locally spread SCCL and SCCLPH by optimization of chemoradiotherapy

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Larynx cancer and laryngopharynx in the general structure of oncopathology occupies the sixth place. Overall and disease-free survival of patients hospitalized for diseases with III-IV stage is 27 and 11 months [3, 6]. The increment of cancer of larynx and laryngopharynx in counties of CIS over the past 10 years was in man in 30.7%, in women – 17,6% [4]. In Ukraine the incidence of cancer larynx and laryngopharynx is 5.6 per 100 thousand population, where the man in 11,4 and 0,6 women per 100 thousand population; cancer mortality larynx and laryngopharynx is 3,2 per 100 thousand population, 6,7 man and 0,2 - women of 100 thousand population. Cancer of this localization is from 1,3% of all malignant tumors of upper respiratory and digestive paths [6]. In accordance literature data disease severity in these patients is caused primarily because of prevalence of process: in stage III-IV are diagnosed in 70,0% of patients who were hospitalized [6, 7, 8]. This is clearly evident

from the fact that among the first ill in Ukraine had stage III 47,7% and IV - 11,7%. For stage III Poltava region 66,7% and IV - 6,0%. Till the 1 year from the time of diagnosis, did not live in Ukraine 27,1% and Poltava region – 23,5%. The low detection on prophylactic examinations that in Ukraine – 17,6% and 9,5% Poltava region has negative impact on these figures [6]. In addition, the performance of surgical intervention in the first stage does not allow to estimate radiosensitivity of tumors, evaluate the possibility of patient to be cured by conservative method and don't make the operation [5]. But till this time does not exist one reasonable methods of diagnosis and treatment of patients with cancer larynx and laryngopharynx [5, 6]. So the purpose of the study to develop new and improve importance of methods of therapy for patients with local advanced cancer of laryngopharynx, especially in case of refuse of patients from operations, as well as of patients hospitalized with contraindications to surgery. The aime of this investigation. To raise efficiency of treatment of patients with locally advanced squamous cell carcinoma of the larynx and laryngopharynx by optimization of chemoradiation treatment, based on the level of expression of immunohistochemical markers as a factor that reflects ongoing efficiency chemoradiation therapy and motivates further course disease.

The materials and methods. All Patients, who participated in the study of (n = 108) had almost identical outgoing data. Thus, at the time of expiration of inspection of each patient was known: age, gender, distribution process for TNM and stage of disease, verification of tumor differentiation degree of tumor and histological characteristics, localization of tumor, tumor growth form, the term started treatment.

Patients were divided by blind method into two groups, depending upon the type of treatment offered each group includes two subgroups. Patients in group I conducted following treatment. In I group 1 subgroup patients received RCT by the classical method in static mode on tumor and regional nodes by classical fields in 2 stages of the three-week break between the phases SD2,6Hr to TAD 65 - 70Hr. In I group 2 subgroup patients received RCT in static mode on tumor and regional nodes classical fields in 2 stages of the three-week break between the stages of multi fractionation daily dose SD 2,6Hr (1,3Hr+1,3Hr) to the TAD 65 - 70Hr. Patients of

group II were divided into 1 and 2 subgroup and received the following treatment. In 1 subgroup patients received poly chemotherapy (PCT) in 2 stages of metronome mode: cisplatin, 5-FU with a three-week break. After three weeks of break started irradiating the classic fractionation in static mode in two stages with a break of 3 weeks of SD 2,6Hr (1,3Hr+1,3Hr) to TAD 65 - 70Hr. Patients of 2 subgroup group II received poly chemotherapy (PCT) in metronome mode: cisplatin, 5-FU (two repeated courses with intervals of 3 weeks of (like in first subgroup). After three weeks of break began irradiation in two stages in static mode with multi fractionation daily doses. at the first stage of radiation therapy along with irradiation was performed third course PCT. Withstanding the interval of 3 weeks of radiation abatement for the reaction were given in the second phase of DHT mode multi fractionation daily doses SD 2,6Hr (1,3Hr 1,3Hr +) to the TAD 65 - 70Hr (106 - 115.5 ed.TDF respectively). The methods of treatment were differed from Group I that group patients II receiving CRT, previously, the study added evaluation of the level of expression of tumor markers Ki-67, Bcl-2 and mp53.

Results. Analyzing the results obtained from the treatment in the I group , take into account the frequency of full and partial regression. They were not the same in both subgroup in I group. Complete regression was subgroup 6 (19,35%) to 3 (12,0%) and differ from one another in 1.6 times ($p < 0,05$), whereby 1 subgroup indicators slightly higher than 2subgroup. Partial regression also showed the best result in 1subgroup, but it was no difference: 8 (25,82%) to 6 (24,0%) 1 and 2, respectively subgroup. As for the stabilization process, the picture is changed 2 showed subgroup best result in 1,86 times - 9 (36,0%) to 6 (19,35%) 2 subgroup and 1 respectively. Progression index also showed better results 11 (35.48%) to 7 (28,0%) subgroup 1 and 2, respectively.

During this investigation it was rate effect from treatment depending on the distribution of process (T). In carrying out DGT as self method for stage T2 effect from the treatment was higher than at T3. Thus, a complete regression at T2 is 4 (16,67%), while T3 5 (15,63%); partial regression at T2 is 9 (37,50%), while T3 5 (15,63%). However, regarding the stabilization process, at T2, this figure better was

10 (41,67%) to T3 in 5 (15,63%). Results of progression generally differ and T2 is at 1 (4,16%) and T3 at 17 (53,12%). This fact confirmed the significance of stage for the expected outcome from treatment and that the result does not depend on method of dose selection, in this case self DGT rate insufficient to overcome the oncological processes. The observed survival in both experiments subgroups also was different for 1 year was 17 (54,84%) 1 subgroup against 18 (72,0%) 2 subgroup. Disease-free process during 1 year was 11 (35,48%) patients vs. 8 (32,0%) patients subgroup 1 and 2, respectively. Three-year overall survival failing it was no difference: 5 (16,13%) 1 subgroup versus 6 (24,0%) 2 subgroup but without relapse patients with difference: 1 (3,23%) to 5 (20,0%) 1 and 2, respectively subgroup that in 6,1 times speaks in favor of the proposed treatment 2 subgroup.

As a result of irradiation of both subgroup I definitely fit the radiation reaction. It may be noted that the use of DGT in the multi fractionation mode daily dose ($p = 0,05$) reduces radiation reaction on skin stage in 4 times in comparison with classical DGT fractionation mode: 16,0% vs. 64,51% 2 group and group 1, respectively. With regard to the mucous membrane of larynx and hypopharynx, this figure is even better: 2 10,34% against 55,56% of group 1, respectively, in 5 times radiation reaction 3 stage in 2 subgroup lower than 1 group. In conclusion of this investigation it possible to say that multi fractionation dose help to decreases the radiation reactions that much weight, but does not affect to increase the overcoming of oncological process. Overall, the results obtained, we can say that a separate exchange of DGT, regardless of the method choosing dose concerning tumor responses to treatment has no difference. These results again demonstrate the necessity of finding new methods to overcome oncological process.

Analyzing the results ,concerning tumor reaction from treatment in II group that complete regression were different and in1 subgroup were 6 (22,22%) compared to 12 patients (48,0%) in 2 subgroup that 2,16 2 times better subgroup. Partial regression have no difference. Stabilization process in subgroup 1 to 2 partial was 8 (29,63%) to 4 (16,0%), in 1.85 times better in the proposed treatment in 2 partial. The same situation concerning progression, which in 2.46 times profitable to indicate a

method of therapy in subgroup 2: 8 (29,63%) to 3 (12,0%) subgroup 1 and 2, respectively.

The total results of survival showed that after 1 year of treatment which all patients received in both groups were alive. However, in 1 subgroup without relapse left 17 (62,96%) patients versus 22 (88,0%) patients subgroup 2, respectively, indicating that in 1,39 times for 2 subgroup treatment method. At the 2 year of observation of survival in 1 subgroup total was 17 (62,96%) compared with 23 (92,0%) patients 2 subgroup was in 1,46 times better than 1subgroup. And patients without recurrence was in 2 times more than in 2 subgroup and in 1 subgroup 13 (52,0%) to 7 (25,93%), respectively. In year 3 observations 2 subgroup still alive 20 (80,0%) patients versus 5 (18,52%) patients in subgroup 1 it says in 4.31 times for treatment carried out in 2 subgroup.

Disease-free period for 3 year has a different and also became 9 (36,0%) to 4 (14,81%) in 2 and 1 subgroup that better in 2.43 in subgroup. Summarizing the foregoing, it can be argued that the most effect, structuring data brings the treatment method which were proposed to patients of 2 subgroup.

Also, confirm that fact and results of immunohistochemistry research. Making the summary of dependence of oncological process from expression Ki-67, Bcl-2 and mp53 performance can be traced middle of tumor markers in subgroups in Fig. 1.

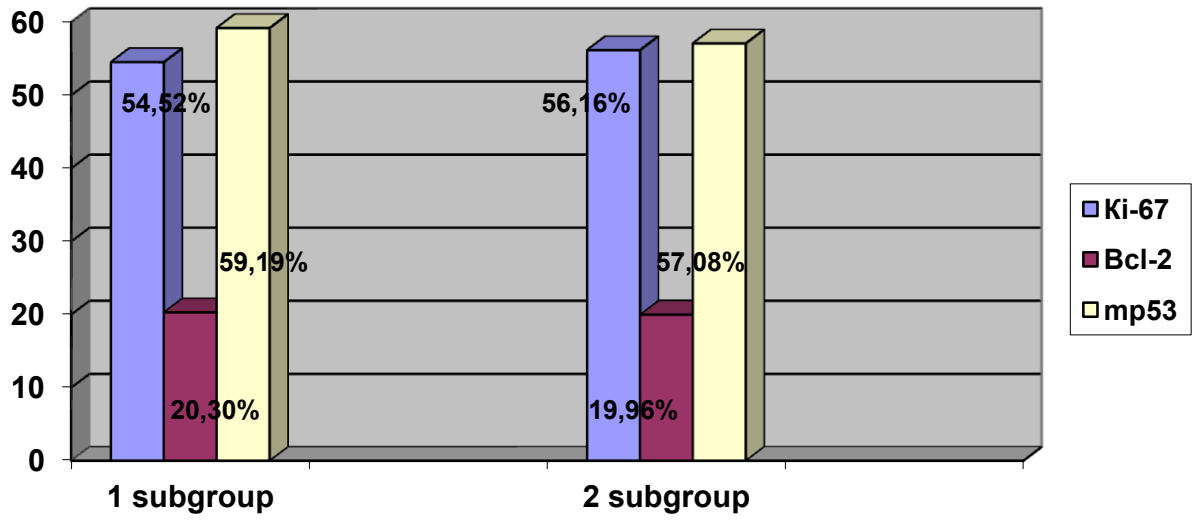


Figure 1. Indicators of expression of oncological markers in subgroups.

Figure 1 shows that the difference in results of expression in both subgroup not observed. But based on the comparison of passing the oncological process in subgroup as suggested by response to treatment methods, give priority to treatment by scheme which were proposed in 2 subgroup. Thus, we can conclude that oncological marker Bcl-2 is one of the mechanisms of low tumor sensitivity to chemo radiation impact, but on the other side is an important predictive marker for possible sensitivity to SCCL and SCCLPH. In our case, this threshold is 20,0% and is common to totally selection  where the best response to treatment of oncological process that allows rely on the figure during the choosing of tactics of treatment. Probably, when tumor markers expression mp53 an average of 60,0% had recurrence garden 1 year surveillance and disease progression. With regard to the positive manifestations of oncological process treatment: surveillance 2 year end and at the time of observation, complete and partial responses, stabilization, it expression of tumor markers mp53 averaged 57,0%. Thus, taking expression mp53 tumor markers in 60,0%, as last high threshold, we can offer CRT, which offered 2 subgroup. As for the level of expression Ki-67, when the average of expression 54 – 55,0% in both groups of treatment effect from in 2 subgroup is probably high. Thus, it may be noted that the higher the level of Ki-67 expression those earlier relapse occurs. However, the higher expression Ki-67, the better the response of tumor to CRT surveillance at our investigation also confirmed the direct dependence on expression Ki-67, higher expression Ki-67, the better surveillance, dependence on these can be based on choosing method of treatment, the known expression of oncological markers.

Thus, we can offer to enter into the necessary diagnostic examination of patients with SCCL and SCCLPH assessment expression of oncological markers mp53, Ki-67, Vcl-2 for the selection of tactics and method of therapy.

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**Ключові слова:** експресія пухлинного маркеру Ki-67, Bcl-2, mp53; плоскоклітинний рак гортані та гортаноглотки, хіміопроменева терапія

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**Keywords:** expression of tumor markers Ki-67, Bcl-2 and mp53, squamous larynx cancer larynx and laryngopharynx, chemoradiotherapy.

## Лікувальний ефект у хворих на місцевопоширений ПРГ та ПРГГ при оптимізації хіміопроменевого лікування

Жукова Т.О., Васько Л.М., Нестуля К.І.

В Україні захворюваність на рак гортані та гортаноглотки становить 5,6 на 100 тис. населення, де чоловіків 11,4, а жінок 0,6 на 100 тис. населення. Метою робити стало бажання підвищити ефективність лікування хворих на місцевопоширений плоскоклітинний рак гортані (ПРГ) та плоскоклітинний рак гортаноглотки (ПРГГ) шляхом оптимізації хіміопроменевого лікування, спираючись на рівень експресії імуногістохімічних маркерів, як фактору, який відображає ефективність проведеної хіміопроменевої терапії та мотивує подальший перебіг захворювання. Аналіз здійснювався вивченням рівню експресії імуногістохімічних маркерів проліферації та апоптозу (mp53, Bcl-2, Ki-67) у пацієнтів, хворих на ПРГ та ПРГГ; визначенням безпосередніх результатів традиційної дистанційної гамма-терапії (ДГТ) при ПРГ та ПРГГ в залежності від імуногістохімічних особливостей пухлини; вивченням безпосередніх результатів запропонованої хіміопроменевої терапії в режимі мультифракціювання дози в залежності від імуногістохімічних особливостей пухлини; вивченням віддалених результатів проведеної променевої та

хіміопроменевої терапії при місцевопоширених ПРГ та ПРГГ. В результаті проведеного дослідження, можно пропонувати ввести в необхідні діагностичні обстеження хворих на ПРГ та ПРГГ оцінку експресії онкомаркерів mp53, Ki-67, Bcl-2 для можливого вибору тактики та методу терапії.

## Лечебный эффект у больных местно-распространенным ПРГ и ПРГГ при оптимизации химиолучевого лечения

Жукова Т.А., Васько Л.Н., Нестуля Е.И.

В Украине заболеваемость раком гортани и гортаноглотки составляет 5,6 на 100 тыс. населения, где мужчин 11,4, а женщин 0,6 на 100 тыс. населения. Целью работы стало желание повысить эффективность лечения больных местно-распространенным плоскоклеточным раком гортани (ПРГ) и плоскоклеточным раком гортаноглотки (ПРГГ) путем оптимизации химиолучевого лечения, опираясь на уровень экспрессии иммуногистохимических маркеров, как фактора, который отображает эффективность проведенной химиолучевой терапии и мотивирует дальнейшее течение заболевания. Анализ осуществлялся изучением уровня экспрессии иммуногистохимических маркеров пролиферации и апоптоза (mp53, Bcl-2, Ki-67) у пациентов, больных ПРГ и ПРГГ; определением конкретных результатов традиционной дистанционной гамма-терапии (ДГТ) при ПРГ и ПРГГ в зависимости от иммуногистохимических особенностей опухоли; изучением непосредственных результатов предложенной химиолучевой терапии в режиме мультифракционирования дозы в зависимости от иммуногистохимических особенностей опухоли; изучением отдаленных результатов проведенной лучевой и химиолучевой терапии при местнораспространенных ПРГ и ПРГГ. В результате проведенного исследования, можно предлагать ввести в необходимые диагностические обследования больных ПРГ и ПРГГ оценку экспрессии онкомаркеров mp53, Ki-67, Bcl-2 для возможного выбора тактики и метода терапии.

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Larynx cancer and laryngopharynx in the general structure of oncopathology occupies the sixth place. Overall and disease-free survival of patients hospitalized for diseases with III-IV stage is 27 and 11 months [H. Hauswald et al., 2011]. Thus, we can conclude that oncological marker Bcl-2 is one of the mechanisms of low tumor sensitivity to chemo radiation impact, but on the other side is an important predictive marker for possible sensitivity to SCCL and SCCLPH. In our case, this threshold is 20,0% and is common to totally selection  where the best response to treatment of oncological process that allows rely on the figure during the choosing of tactics of treatment. Probably, when tumor markers expression mp53 an average of 60,0% had recurrence garden 1 YEAR surveillance and disease progression. With regard to the positive manifestations of oncological process treatment: surveillance 2 YEAR end and at the time of observation, complete and partial responses, stabilization, it expression of tumor markers mp53 averaged 57,0%. Thus, taking expression mp53 tumor markers in 60,0%, as last high threshold, we can offer CRT, which offered 2 subgroup. Thus, it may be noted that the higher the level of Ki-67 expression those earlier relapse occurs. However, the higher expression Ki-67, the better the response of tumor to CRT surveillance at our investigation also confirmed the direct dependence on expression Ki-67, higher expression Ki-67, the better surveillance, dependence on these can be based on choosing method of treatment, the known expression of oncological markers. Thus, we can offer to enter into the necessary diagnostic examination of patients with SCCL and SCCLPH assessment expression of oncological markers mp53, Ki-67, Vcl-2 for the selection of tactics and method of therapy.