КЛІНІЧНА ТА ПРОФІЛАКТИЧНА МЕДИЦИНА

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THERAPEUTIC EFFECT OF IMPROVED CHEMORADIOTHERAPY IN PATIENTS WITH LOCALLY SPREAD SQUAMOUS CELL CARCINOMA OF PHARYNX AND PHARYNGOLARYNX

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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.

Key words: expression of tumour markers Ki-67, Bcl-2 and mp53, squamous cancer of larynx and laryngopharynx, chemoradiotherapy.

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Introduction

Cancer of larynx and laryngopharynx ranks the 6th position in the general structure of cancerous diseases. Overall five-year survival time among the patients with the diseases caught in III-IV stage ranges from 11 to 27 months [3, 6]. The growth of laryngeal and laryngopharyngeal cancer over the past decade made up 30.7% in men and 17,6% in women [4]. In Ukraine the incidence of cancer of larynx and laryngopharynx is 5.6 per 100 thousand population, mortality rate caused by laryngeal and laryngopharyngeal cancer is 3,2 per 100 thousand population. Cancer of this localization constitutes 1,3% of all malignant tumours of upper respiratory and digestive passages [6]. According to the relevant data the disease severity of these patients is caused primarily by the volume o cancerous expansion: 70,0% of patients who were hospitalized were diagnosed to have the disease in stage III-IV [6, 7, 8].

This is clearly evident from the fact that in Ukraine among the patients with the disease diagnosed first, 47,7% have stage III and 11,7% have stage IV. In Poltava region, stage III was diagnosed in 66,7% and stage IV – in 6,0% of the patients. In Ukraine, 27,1% did not live up to a year, while in Poltava region this proportion equalled about 23,5%. There is low detection of this pathology during prophylactic check-ups in Ukraine, about 17,6% of cases, and 9,5% of cases in Poltava region that has negative impact on the outcomes of the diseases [6]. Moreover, the surgical intervention in the stage does not allow us to estimate radio sensitivity of tumours, i.e. to evaluate the response of the patient to the conservative treatment and to avoid surgery [5].

Low values of remote treatment results after remote gamma-therapy (RGT) as a separate approach in the cancer treatment necessitate in searching for effective ways in overcoming tumour radio-resistance and protecting healthy tissues. For this purposes, the variety of treatment options can be recommended, including a combination of radiotherapy and chemotherapy, though complications following this treatment are quite common, up to 57%. The sequence of radiotherapy and chemotherapy as well the efficiency of various schemes of chemotherapy are still disputable.

Despite definite success in this particular field,

the results presented in numerous researches are discussible and demand in-dept careful studying. According to various available sources, the patients with locally spread squamous cell carcinoma of pharynx and pharyngolarynx (stage III-IV) have to undergo combined treatment including induction chemotherapy (IC), radiotherapy (RT) with or without surgical intervention. But reasonable uniform methods and approaches regarding the diagnosis and treatment of the patients with cancer of larynx and laryngopharynx do not exist [5, 6]. Thus, the studies aimed at the development of new techniques and to improve existing methods of therapy for cancerous patients, especially in cases of patients' refusal from the surgical operations, as well as in cases when a surgery is contraindicated. The aim of this study is to increase efficiency of treatment of patients with locally spread squamous cell carcinoma of pharynx and pharyngolarynx by improving chemoradiotherapy based on the level of expression of immunohistochemical markers as a factor that reflects ongoing efficiency chemoradiation therapy and predetermines the further course of the disease.

Materials and methods

All patients involved in the study of (n = 108) had almost identical outgoing data, which significantly did not differ. Thus, at the moment of finishing medical check-up the information about of each patient included age, sex, volume of cancer extension by TNM and the stage of the disease, verification of tumour, tumour differentiation degree and histological characteristics, tumour localization, tumour growth form, the term when treatment started.

Patients were divided by blind method into two groups depending on the type of treatment offered to each group, which, in turn, was divided into two subgroups. The patients in group I underwent the following treatment. The patients of the I group, 1 subgroup, received RCT by the standard technique in static mode directed on tumour and regional lymph nodes by conventional fields in 2 stages with the three-week break between the phases SD2,6Hr to TAD 65 - 70Hr. The patients of the I group, 2 subgroup received RCT in static mode on tumour and regional nodes by conventional fields in 2 stages with 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 subgroups and received the following treatment. The 1 subgroup received poly chemotherapy (PCT) in 2 stages of metronome mode: cisplatin, 5-FU with a three-week break. After three weeks of break we 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.

The patients of subgroup 2, 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 we 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. Keeping the interval of 3 weeks to lower the response to radiation, we conducted the second phase of GCT mode multi fractionation with daily doses SD 2,6Hr (1,3Hr 1,3Hr +) to the TAD 65 - 70Hr (106 - 115.5 ed.TDF respectively). The methods of treatment differed from the group I as the patients of group II received CRT, and in previous study we evaluated the level of expression of tumour markers Ki-67, Bcl-2 and mp53.

Results

Analyzing the results obtained from the treatment in I group we took into account the frequency of full and partial regression. They were not the same in both subgroup in I group. Complete regression in the group I made up 6 cases (19,35%) to 3 (12,0%) and differed in 1.6 times ($p < 0,05$), whereby 1 subgroup indicators were slightly higher than in the 2 subgroup. Partial regression also showed better result in 1 subgroup, but it did not differ significantly: 8 (25,82%) to 6 (24,0%) 1 and 2 subgroups respectively. As for the process stabilization, the picture changed, and 2 subgroup showed better result in 1,86 times: 9 (36,0%) to 6 (19,35%) in 2 and 1 subgroup respectively. Progression index also showed better results, 11 (35.48%) to 7 (28,0%) in subgroups 1 and 2, respectively.

During this investigation we evaluated direct effect of the treatment depending on the process of cancer extension (T). The effect obtained by DGT at stage T2 was higher than at T3. Thus, a complete regression at T2 was 4 (16,67%), while at T3, it was 5 (15,63%); partial regression at T2 made up 9 (37,50%), while at T3, it was 5 (15,63%). However, regarding the stabilization process, at T2, the figures were better, 10 (41,67%) to 5 (15,63%) at T3 . Results of progression differed, and at T2 it was 1 (4,16%), and at T3 it was 17 (53,12%). This confirmed the significance of stage in outcome prognosis and expectations and the fact that result does not depend on method of dose selection, and a separate use of DGT is insufficient to overcome the oncological processes. We noticed the survival in both subgroups did not different and was 17 (54,84%) 1 subgroup against 18 (72,0%) 2 subgroup for a year period. Disease-free process during 1 year was registered in 11 (35,48%) patients vs. 8 (32,0%) patients in the subgroup 1 and 2, respectively. Three-year overall survival did not differ significantly: 5 (16,13%) 1 subgroup vs. 6 (24,0%) 2 subgroup, while the course without relapse differed: 1 (3,23%) to 5 (20,0%) in 1 and 2 subgroups, respectively.

We also analyzed the consequences and responses caused by irradiation in both subgroups of I group. It may be noted that the use of RGT in the multi fractionation mode daily dose ($p = 0,05$) re-

duces skin reaction at T3 in 4 times in comparison with standard RGT fractionation mode: 16,0% vs. 64,51% in 2 and 1 groups, respectively. The mucous membrane of larynx and hypopharynx, this figure is even better: 10,34% of group 2 vs. 55,56% of group 1, i.e. radiation reaction at stage 3 in 2 subgroup is lower than in 1 group in 5 times. We can conclude that multi fractionation dose helps to decreases the radiation reactions that is important, but does not contribute in overcoming cancerous process. In general, the results obtained showed that a separate RGT, regardless of the method of dose administration and concerning tumour responses to treatment, has no difference. These results demonstrate the necessity of finding new methods to combat cancer.

Analyzing the results concerning tumour response to the treatment in II group that total egressions were different, and in 1 subgroup they were 6 (22,22%) compared to 12 patients (48,0%) in 2 subgroup that was 2,16 times better in the 2 subgroup. Partial regressions had no significant difference. Stabilization process observed in subgroup 1 vs. subgroup 2 made up 8 (29,63%) to 4 (16,0%), that was in 1.85 times better in the treatment proposed for the subgroup 2 .

The results of total survival showed that all patients received in both groups received the treatment reached one year survival period. 17 (62,96%) patients in subgroup 1 had no relapses vs. 22 (88,0%) patients in subgroup 2. During the 2nd year of the observation, the survival in 1 subgroup total was 17 (62,96%) cases compared with 23 (92,0%) cases in subgroup 2, that was in 1,46 times better than in the 1 subgroup. The patients without recurrence in 2 subgroup prevailed as much as twice this value in 1 subgroup, 13 (52,0%) to 7 (25,93%), respectively. During the 3rd year of the observations 20 (80,0%) patients of the 2 subgroup survived vs. 5 (18,52%) patients in subgroup 1.

Disease-free period for the 3 year was significantly different and constituted 9 (36,0%) cases vs. 4 (14,81%) in 2 and 1 subgroup, respectively. Summarizing the data obtained, we can conclude, the treatment method proposed to patients of subgroup 2 was the most effective. This conclusion was also confirmed by the findings of immunohistochemical tests. Drawing the conclusion regarding the dependence of cancer process on the expression Ki-67, Bcl-2 and mp53 performance we can trace mean values of tumour markers in the subgroups, shown in Fig. 1.

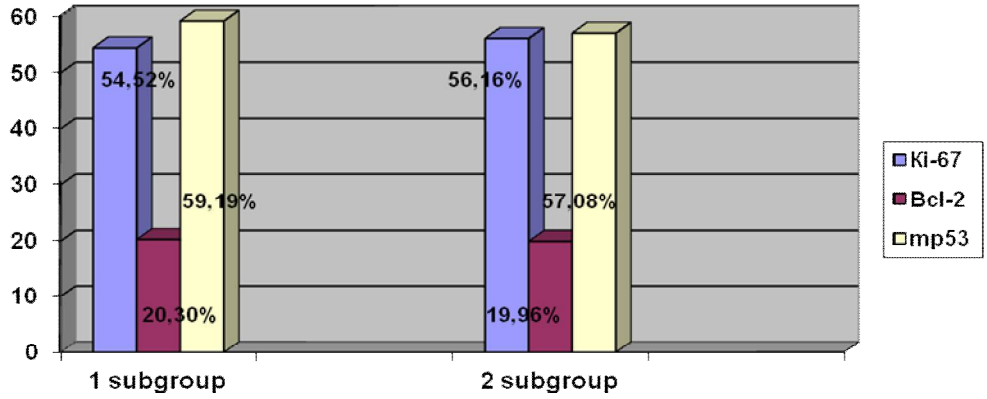

Figure 1. Indicators of oncologic markers expression in subgroups.

Figure 1 shows that there is no significant difference in the results of expression in both subgroups. But based on the results obtained by comparing the course of the cancerous process in the subgroups and their responses to the treatment methods, the treatment scheme were proposed to the subgroup 2 was assesses as more effective. Thus, we can conclude that cancer marker Bcl-2 is one of the mechanisms of low tumour sensitivity to chemo radiation impact, but on the other side it is an important predictive marker for possible sensitivity to chemo radiotherapy for spread squamous cell carcinoma of pharynx and pharyngolarynx. In our case, this sensitivity threshold makes up 20,0% and is common trough all sampling.

Probably, when tumour markers expression mp53 was an average of 60,0%, we registered the disease recurrence and progression during the 1st year. A for the positive manifestations of cancerous process treatment, we should stress the surveillance for the 2 year and at the time of observation, complete and partial responses to the treatment, stabilization, and expression of tumour markers mp53 was an average 57,0%. Thus, taking expression mp53 tumour markers of 60,0% as the highest threshold, we can offer CRT, used for the subgroup 2. As for the level of expression Ki-67, when the average of expression was 54 – 55,0% in both groups, the treatment effect in the subgroup 2 was probably high.

Thus, it may be noted the higher the level of Ki-67 expression the earlier relapse occurs. However, the higher expression Ki-67, the better the response of tumour to chemoradiotherapy and better surveillance, that confirms the direct dependence on expression Ki-67. These results can be taken into account when selecting the proper tactics of treatment.

Thus, we can offer to implement the assessment of expression of cancer markers mp53, Ki-67, Vcl-2 as an important diagnostic test into practice in order to select best tactics of the therapy.

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Реферат

ЛІКУВАЛЬНИЙ ЕФЕКТ У ХВОРИХ НА МІСЦЕВОПОШИРЕНИЙ ПРГ ТА ПРГГ ПРИ ОПТИМІЗАЦІЇ ХІМІОПРОМЕНЕВОГО ЛІКУВАННЯ

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

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 роботи 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, Кі-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, можна пропонувати ввести в необхідні діагностичні обстеження хворих на ПРГ та ПРГГ оцінку експресії онкомаркерів mp53, Кі-67, Bcl-2 для можливого вибору тактики та методу терапії.

Реферат

ЛЕЧЕБНЫЙ ЭФФЕКТ У БОЛЬНЫХ МЕСТНО-РАСПРОСТРАНЕННЫМ ПРГ И ПРГГ ПРИ ОПТИМИЗАЦИИ ХИМИОЛУЧЕВОГО ЛЕЧЕНИЯ

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Ключевые слова: экспрессия опухолевого маркера Ki-67, Bcl-2 и mp53; плоскоклеточный рак гортани и гортаноглотки, химиолучевая терапия.

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.