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INFLUENCE OF CONFORMAL RADIOTHERAPY IN COMBINATION WITH RADIOMODIFIERS ON THE CONTENT OF VEGF, COX-2, AND PGE-2 IN BLOOD SERUM OF PATIENTS WITH HEAD AND NECK SQUAMOUS CELL CARCINOMA

Background. The development of new approaches to modeling tumor radiosensitivity in patients with head and neck squamous cell carcinoma (HNSCC) is an important problem for overcoming tumor radioresistance. New agents for radiomodification are inhibitors of the enzyme cyclooxygenase-2 (COX-2). The study of markers of radioresistance in cancer patients undergoing radiotherapy (RT) in combination with COX-2 inhibitors and chemotherapy may contribute to the effectiveness of RT. **Aim**. To determine the effect of conformal RT in combination with radiomodifiers (celecoxib, cisplatin, or their combination) on the content of vascular endothelial growth factor (VEGF), COX-2, and prostaglandin E-2 (PGE-2) in the serum of patients with HNSCC. **Materials and Methods**. 47 patients with HNSCC were divided into 4 groups: RT in combination with celecoxib and cisplatin, RT with cisplatin, RT with celecoxib, and RT. Patients received radiation treatment on a Clinac 600C linear accelerator. The levels of VEGF, COX-2, and PGE-2 in the serum were determined by enzyme immunoassay. **Results**. Blocking COX-2 in patients with HNSCC leads to a decrease in VEGF levels. The largest decrease in VEGF levels was observed in a group treated by RT in combination with celecoxib and cisplatin, indicating a more effective antiangiogenic effect. The changes in the levels of VEGF, COX-2, and PGE-2, which are most pronounced under the combined effect of RT and both radiomodifiers, coincided with an objective response to radiation treatment. **Conclusions**. The data obtained indicate the effect of radiomodification on the suppression of angiogenesis, which is most pronounced under the combined effect of RT and both radiomodifiers. The decrease in the levels of PGE-2, COX-2, and VEGF coincides with the clinical efficacy of radiotherapy according to RECIST 1.1 criteria.

Keywords: head and neck squamous cell carcinoma, radiation therapy, COX-2 inhibitor, cisplatin, vascular endothelial growth factor, cyclooxygenase-2, prostaglandin E-2.

For several decades, head and neck squamous cell carcinoma (HNSCC) has been a leading cause of morbidity in most countries of the world, with the number of cases of neoplasms in the main localizations reaching 54%—68% [1]. The combined HNSCC treatment is usually applied, i.e., radiotherapy (RT)

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and surgery. Often, taking into account the general condition (according to the ECOG scale), in such patients, RT is the only type of medical care. The vast majority (97%—99%) of HNSCC requires large total focal doses (TFD, 70 Gy or more), which negatively affects surrounding healthy organs and tissues. Increasing TFD increases the effectiveness of treatment, but also leads to significant radiation-dependent complications [2]. Accordingly, one of the urgent problems in radiation oncology is to overcome radioresistance without further dose increase. Along with the improvement of the irradiation modes, technologies, and technical means, selective management of tumor radiosensitivity using radiomodification with various radiosensitizing agents is becoming increasingly important. Therefore, it seems reasonable to develop new approaches for targeted modeling of tumor radiosensitivity in cancer patients. Recently, the study of the main mechanisms of tumor radiosensitization has made it possible to identify areas for the use of new targeted therapeutic agents to optimize RT methods: blocking signaling pathways; inhibition of DNA repair; cell cycle synchronization; induction of apoptosis; inhibition of tyrosine kinases; inhibition of cyclooxygenase-2 (COX-2); effects on angiogenesis, etc. [3—5]. In this regard, the search for new RT technologies for HNSCC is relevant and obvious.

Overexpression of COX-2, an enzyme that catalyzes the conversion of arachidonic acid to prostaglandin E-2 (PGE-2), which plays an important role at all stages of oncogenesis, is considered one of the main causes of chemoradiotherapy resistance. Tumors with COX-2 overexpression lose their ability to apoptosis and activate neoangiogenesis, which leads to an unfavorable prognosis. Currently, COX-2 is considered an important target for anticancer therapy [6—8]. COX-2 inhibitors as radiomodifiers in combination with X-rays suppress the tumor cell proliferation more effectively than each of them alone due to inhibition of angiogenesis [9]. At the same time, the radiosensitizing effect of COX-2 inhibitors on normal tissues was not detected, which is important for expanding the limits of the RT interval and their practical use in radiation oncology [10—12].

Many researchers have proven the feasibility of using cytostatics to radiomodify malignant tumors. In particular, the cytostatic agent cisplatin is the "gold standard" for the treatment of head and neck cancer [13]. Cisplatin, as a radiosensitizer, is recommended by the National Cancer Institute (NCI, USA), the National Comprehensive Cancer Network (NCCN, USA), and the European Society for Medical Oncology (ESMO) [14]. As a radiosensitizer, it shows a synergistic effect with radiation on tumor cells. When it is used simultaneously with radiation, the number of dead cells increases, and tumor growth is more effectively controlled [15]. Thus, the combined use of non-steroidal anti-inflammatory drugs (COX-2 inhibitors) and cytostatics is a new opportunity to improve the results of RT of malignant tumors, in particular, HNSCC, by enhancing the antitumor effect through synergy, or additivity, or potentiation of effects [16]. In this regard, it is relevant and important to study the role of COX-2 inhibitors in combination with cytostatics in radiomodification to develop new technologies for individualizing RT of patients with COX-2-positive HNSCC.

The mechanisms of radiosensitization via the combined action of selective COX-2 inhibitors and cytostatics remain virtually unexplored. The radiation regimens under which the combined effect is most effective have not been determined. The effect of RT in combination with various radiomodifiers on the content of vascular endothelial growth factor (VEGF), COX-2, and PGE-2 in the blood serum of cancer patients is not sufficiently understood. This delays the development of new methods to optimize RT for head and neck cancer [17].

The aim of the study was to determine the effect of conformal RT in combination with various radiomodifiers (celecoxib, cisplatin, or their combination) on the content of VEGF, COX-2, and PGE-2 in the serum of HNSCC patients.

Materials and Methods

In 2019—2023, 47 patients with HNSCC aged 50 to 79 years (median age 61 years) were examined and treated at the State Institution "Grigoriev Institute of Medical Radiology and Oncology of the National Academy of Medical Sciences of Ukraine". Patients were informed about the study and agreed to participate in it. The Committee on Bioethics and Deontology of the State Institution "IMRO NAMS of Ukraine" (Protocol No. 10 of 03.11.2022) approved that the study was conducted in accor-

dance with the relevant laws and regulations, and therefore the results are ethically valid.

Patients were divided into groups depending on different treatment regimens. 10 patients received a course of RT on the Clinac 600C linear accelerator (classical fractionation mode was used, the total focal doses were 60—70 Gy) in combination with celecoxib 100 mg per day and cisplatin (EBEWE, Austria) 30 mg/m^2 per week up to a total dose (TD) of 200 mg (group 1), 11 patients received a course of RT in combination with cisplatin (group 2), 7 patients received a course of RT in combination with celecoxib (group 3), and 19 patients received a course of RT- retrospective analysis (group 4) [4].

The general condition of the patients before the start of RT was 0—1 points on the ECOG scale. In most patients of all groups (64.3%), the general condition, according to the ECOG scale, was estimated at point 1. All patients with HNSCC received morphologic confirmation of the diagnosis after a biopsy of the tumors, as well as an X-ray examination of the chest, abdomen, pelvis, and brain using a Toshiba Aquilon 64 computed tomography scanner to detect the extent of the process, regional lymph node involvement, and distant metastatic process.

When analyzing the extent of the tumor process, it was found that the prevailing number of HNSCC patients (56.0%) had a locally advanced stage of the disease (stage III—IV). It should be noted that there were no patients with distant metastases (M1) among patients with stage IV. Patients with stage I—II disease were in all groups with the same percentage. Among the localizations, laryngeal cancer prevailed (42.9%, 12 out of 28 patients), oropharyngeal tumors were in second place (28.6%, 8 out of 28 patients), and oral tumors were diagnosed in 21.4% of cases (6 patients). The group 2 included two patients (7.1%) with sinus cancer.

The content of VEGF, COX-2, and PGE-2 in the blood serum of patients with HNSCC was determined by enzyme-linked immunosorbent assay (ELISA) using standard reagent kits "VEGF ELISA Kit, Elabscience Biotechnology Inc." (USA); "Invitrogen COX-2 ELISA Kit, Elabscience Biotechnology Inc." (USA); "Prostaglandin D2 ELISA Kit, Elabscience Biotechnology Inc." (USA). The standardized methods for determining VEGF, COX-2, and PGE-2 are based on the use of a "sandwich" version of a solid-phase enzyme-linked immunosorbent assay. Blood samples were taken from patients before and after RT. 5 mL of blood was centrifuged at 3,000 rpm for 15 min, then the serum was frozen and stored at –20 °C. Measurements were performed on a semi-automatic enzyme-linked immunosorbent assay analyzer «Immunochem-2100, HTI" (USA). Tumor regression was assessed according to RECIST 1.1 criteria based on the control computed tomography performed 6—8 weeks after the end of treatment.

Statistical analysis of the data was performed using the statistical software package Statistica for SCCN and parametric (Student-Fisher) and nonparametric methods for small samples. The data were presented as the median and compared between the groups using the Wilcoxon test when comparing paired samples. The difference was considered statistically significant at $p < 0.05$.

Results and Discussion

The content of VEGF, COX-2, and PGE-2 in the blood serum was studied in 47 patients with HNSCC in the dynamics of RT under different treatment regimens.

Table 1 shows the levels of VEGF, COX-2, and PGE-2 in the blood serum of patients with HNSCC in the dynamics of radiation therapy under different treatment regimens, before and after treatment. We revealed that after treatment, the level of VEGF in group 1 decreased by 2.6 times, in group 2 — 1.1 times, in group 3 — 1.9 times, and in group 4 — 1.2 times. That is, the greatest decrease in VEGF levels was observed when RT was combined with celecoxib and cisplatin. After treatment, the level of COX-2 in group 1 decreased by 2.2 times, in group 2 — 1.1 times, in group 3 — 2.2 times, and in group 4 — 1.1 times, and the level of PGE-2 in group 1 decreased by 2.5 times, in group 2 — 1.1 times, in group 3 — 1.8 times, and in group 4 — 1.1 times.

In our previous studies, we determined the dynamic changes in VEGF, COX-2, and PGE-2 levels in the serum of HNSCC patients during RT against the background of an objective response to treatment [18]. In the present research, we aim to study the content of these molecules after the application of conformal RT in combination with various radiomodifiers.

The analysis of the data on different radiotherapy regimens using radiomodifiers in patients with HNSCC showed that changes in the level of VEGF

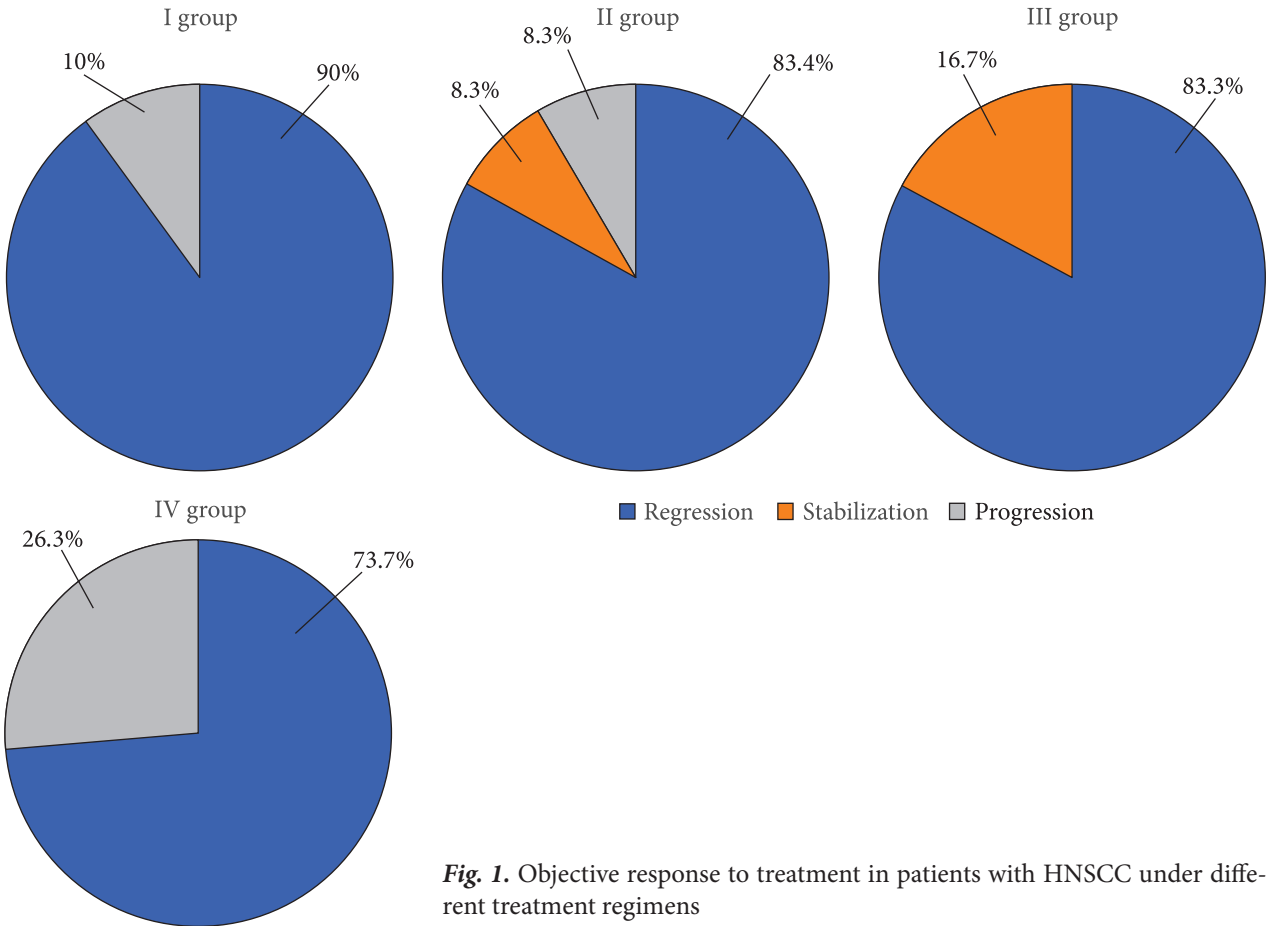

Fig. 1. Objective response to treatment in patients with HNSCC under different treatment regimens

are more pronounced under the combined effect of radiation, cisplatin, and celecoxib, which indicates a slowdown of angiogenesis. Taking into account the literature data, this can be explained by the combined effect of celecoxib and cisplatin. It is known that the COX-2 inhibitor (celecoxib) catalyzes the conversion of arachidonic acid to PGE-2, which plays an important role at all stages of carcinogenesis, in particular, it activates angiogenesis and inhibits apoptosis. Blocking COX-2 leads to a decrease in the level of prostaglandins and the proangiogenic factor VEGF, and enhances anti-angiogenic effects. The action of cisplatin results in the cross-linking of DNA strands and disruption

Table 1. **Levels of VEGF, COX-2, and PGE-2 in the blood serum of patients with HNSCC in the dynamics of different schemes of radiotherapy**

Parameter	Examination period	RT + celecoxib + cisplatin (Group 1, n = 10)		RT + cisplatin (Group 2, n = 11)		RT + celecoxib (Group 3, n = 7)		RT (Group 4, n = 19)	
		n	median	n	median	n	median	n	median
VEGF, pg/mL	before treatment	10	439.3	11	447.5	7	432.4	19	430
	after treatment	10	170.2*	11	398.4	7	226.8*	19	369
COX-2, ng/mL	before treatment	10	68.2	11	67.7	7	71.2	19	70.8
	after treatment	10	31.0*	11	61.6	7	32.1*	19	63.0
PGE-2, pg/mL	before treatment	10	569.8	11	506.4	7	612.2	19	668.0
	after treatment	10	228.5*	11	449.7	7	347.5	19	621.0

Notes: * The difference between pre- and post-treatment values is significant, $p < 0.05$ (Wilcoxon test).

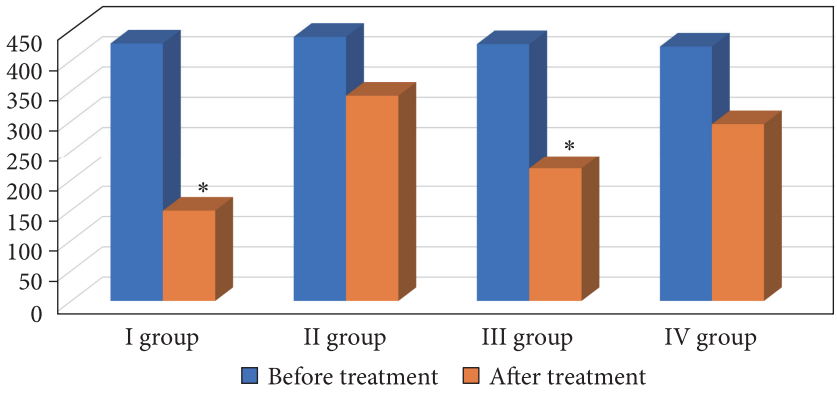

Fig. 2. VEGF content in the dynamics of different radiation therapy regimens in patients with HNSCC depending on the regression of the tumor process, pg/mL. * Significance of differences between the values before and after treatment, $p < 0.05$ (Wilcoxon test)

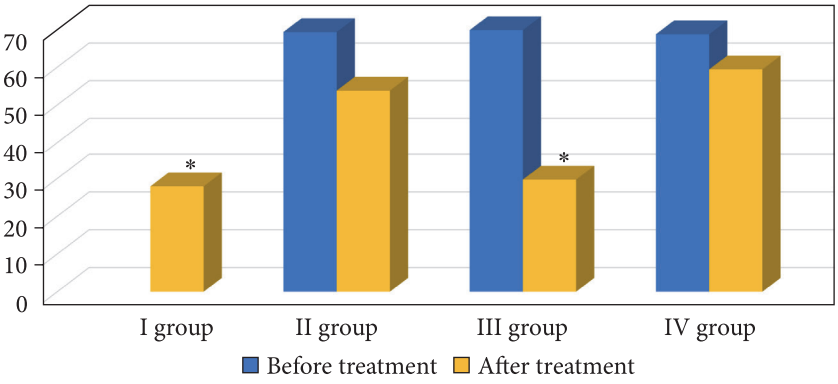

Fig. 3. COX-2 content in the dynamics of different radiation therapy regimens in patients with HNSCC depending on the regression of the tumor process, ng/mL. * Significance of differences between the values before and after treatment, $p < 0.05$ (Wilcoxon test)

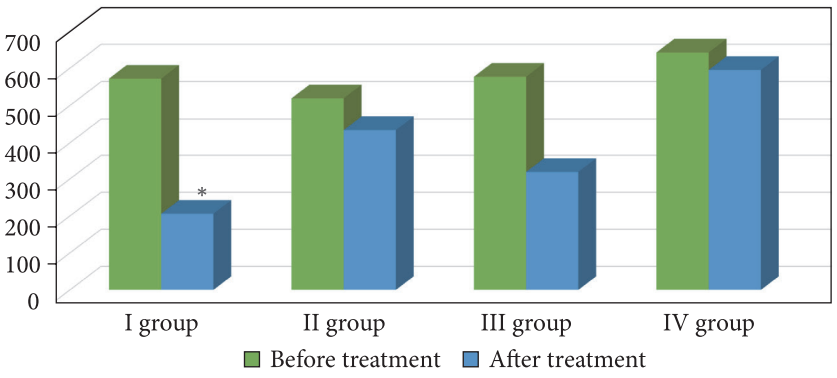

Fig. 4. The content of PGE-2 in the dynamics with different radiation therapy regimens in patients with HNSCC depending on the regression of the tumor process, pg/mL

of its structure, inhibition of DNA synthesis, the arrest of mitosis, and ultimately apoptosis of tumor cells [19]. On the other hand, cisplatin affects the metabolism of arachidonic acid, which affects the activity of COX-2, a key enzyme in the synthesis of PGE-2 [20]. Therefore, the use of cisplatin in combination with a COX-2 inhibitor can enhance the anticarcinogenic effect.

In patients with HNSCC, we analyzed the changes in serum levels of VEGF, PGE-2, and COX-2 depending on the objective response to treatment, which was used to assess the direct effect of RT one month after treatment.

Fig. 1 shows the frequency of objective response to treatment (regression, stabilization, progression) in patients with HNSCC. As seen, the regression of the tumor process is observed in 90% of patients in group 1, 83.4% — in group 2, 83.3% — in group 3, and 73.7% — in group 4.

Therefore, we further analyzed the content of VEGF, COX-2, and PGE-2 in different RE regimens in patients with HNSCC depending on the tumor regression. Changes in serum VEGF levels (Fig. 2) showed that with complete or partial regression, the level of VEGF in group 1 decreased by 2.9 times, in group 2 — by 1.3 times, in group 3 — by 1.9 times, and in group 4 — by 1.4 times. The changes in the levels of COX-2 and PGE-2 in the blood serum depending on the regression of the tumor process are shown in Figs. 3 and 4. As shown, in group 1,

the levels of COX-2 decreased by 2.4 times, and PGE-2 — by 2.8 times compared to the pretreatment levels. In group 2, these indicators decreased slightly, in group 3, COX-2 — by 2.3 times, and PGE-2 — by 1.8 times, and in group 4, these indicators remained practically unchanged. So, in patients with HNSCC who received RT in combination with celecoxib and cisplatin, the greatest decrease in the levels of VEGF, COX-2, and PGE-2 was determined compared with the other treatment regimens in the regression of the tumor process.

Analysis of the results showed that changes in the levels of VEGF, COX-2, and PGE-2 coincided with an objective response to RT. Thus, in the case of tumor regression, a significant decrease in these parameters is observed, more significant with RT in combination with celecoxib and cisplatin, which indicates the effectiveness of this treatment regimen.

The data presented suggest that most patients with HNSCC have increased COX-2 activity and increased PGE-2 synthesis before RT. The results of this study are confirmed by other authors who have shown that transformed cells possess increased levels of COX-2 [10] that do not decrease significantly under the influence of RT [21].

In conclusion, our results indicate that the most effective treatment for patients with HNSCC is RT in combination with celecoxib and cisplatin and therefore open up a new opportunity to optimize radiation treatment of HNSCC.

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ВПЛИВ КОНФОРМНОЇ ПРОМЕНЕВОЇ ТЕРАПІЇ В ПОЄДНАННІ
З РІЗНИМИ РАДІОМОДИФІКАТОРАМИ НА ВМІСТ VEGF, ЦОГ-2 ТА ПГЕ-2
У СИРОВАТЦІ КРОВІ ХВОРИХ НА ПЛОСКОКЛІТИННИЙ РАК ГОЛОВИ ТА ШИЇ

Стан питання. Розробка нових підходів моделювання радіочутливості пухлин у хворих на плоскоклітинний рак голови та шиї (ПРГШ) є важливою проблемою для подолання радіорезистентності пухлин. Новими агентами для радіомодифікації променевої терапії (ПТ) є інгібітори ферменту циклооксигенази-2 (ЦОГ-2). Вивчення маркерів радіорезистентності в онкологічних хворих під впливом променевої терапії в поєднанні з інгібіторами ЦОГ-2 та хіміопрепаратами є сьогодні актуальним і може сприяти підвищенню ефективності променевої терапії. **Мета роботи**. Визначити вплив конформної променевої терапії в поєднанні з різними радіомодифікаторами (целекоксиб, цисплатин або їх комбінація) на вміст фактора росту ендотелію судин (VEGF), ЦОГ та простагландину Е-2 (ПГЕ-2) у сироватці крові хворих на плоскоклітинний рак голови та шиї. **Матеріали та методи**. Обстежено та проліковано 47 хворих на ПРГШ, яких за схемами лікування було поділено на чотири групи: ПТ у поєднанні з целекоксибом та цисплатином, ПТ з цисплатином, ПТ з целекоксибом та ПТ. Хворі отримували курс променевого лікування на лінійному прискорювачі Clinac 600C. Використовувався режим класичного фракціонування. Цисплатин призначали у дозі 30 мг/м^2 на тиждень, целекоксиб — у дозі 100 мг на добу. Рівні VEGF, ЦОГ-2 та ПГЕ-2 у сироватці крові хворих на ПРГШ визначали методом імуноферментного аналізу до та після лікування. **Результати**. Лікування хворих на ПРГШ з блокуванням ЦОГ-2 веде до зниження рівня VEGF. Найбільше зниження рівня VEGF спостерігається при ПТ у поєднанні з целекоксибом та цисплатином, що вказує на більш ефективний антиангіогенний вплив на злоякісну пухлину. Зміни рівнів VEGF, ЦОГ-2 та ПГЕ-2, які найбільш виражені за поєднаної дії ПТ та обох радіомодифікаторів, збігалися з об'єктивною відповіддю на променеве лікування. **Висновки**. Показано вплив радіомодифікації на пригнічення процесу ангіогенезу, який найбільш виражений за поєднаної дії ПТ та обох радіомодифікаторів. Зниження рівнів ПГЕ-2 , ЦОГ-2 та VEGF збігається з клінічною ефективністю променевої терапії за критеріями RECIST 1.1.

Ключові слова: плоскоклітинний рак голови та шиї, променева терапія, інгібітор ЦОГ-2, цисплатин, фактор росту ендотелію судин, циклооксигеназа-2, простагландин Е-2.