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The Effectiveness of Neoadjuvant Chemotherapy Prior to Proton Beam Therapy for Head and Neck Tumors

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ABSTRACT

BACKGROUND: *Malignant tumors of the head and neck are a significant problem in modern oncology, as they occupy an important place in the structure of morbidity and mortality of the population. According to the Ministry of Health of the Russian Federation, 674,587 new cases of malignant neoplasms were registered in 2023, of which 25,038 cases were tumors of the head and neck.* ***AIM:*** *of the study was to evaluate the effect of induction drug therapy on the treatment outcomes of patients with locally advanced tumors of the head and neck who received radiation treatment using proton therapy, IMPT technique (intensity modulated proton therapy).* ***METHODS:*** *The retrospective study included an analysis of the medical records of 103 patients with head and neck tumors, who were divided into two groups: patients who received induction chemotherapy followed by proton chemoradiotherapy (n=50), and patients who did not receive induction antitumor treatment before starting proton chemoradiotherapy (n=53). T-tests for independent samples were used to assess differences between patient groups. The statistical significance of the differences was considered at a level of p <0.05.* ***RESULTS:*** *The median follow-up was 13.4 months (IQR: 11.6–21.6 months). The average follow-up time was 15.7±7.8 months. In the group of monitored patients, none interrupted planned treatment, and therapy was completed on time. In the induction chemotherapy followed by proton chemoradiation therapy group, the average OS was 27.65 months (95% CI: 24.46–30.85), while for the proton chemoradiation therapy groups it was 27.27 months (95% CI: 22.15–31.72), which was a statistically insignificant difference (Chi-squared 0.776, p=0.378). The median OS for both study groups was not reached. The progression-free survival assessment showed that the average time to progression in the induction chemotherapy followed by proton chemoradiation therapy group was 23.1 months (95% CI: 19.6–26.6), versus 21.2 months (95% CI: 16.7–25.7) in the proton chemoradiation therapy group. The incidence of grade 1 leukopenia was 30% in the induction chemotherapy followed by proton chemoradiation therapy group versus 20.8% in the proton chemoradiation therapy group, the incidence of grade 3 disorders was 26% in the induction chemotherapy followed by proton chemoradiation therapy group and 11.3% in the proton chemoradiation therapy group, and grade 3 complications were noted only in the induction chemotherapy followed by proton chemoradiation therapy group (12%). These differences are statistically significant (p <0.01).* ***CONCLUSION:*** *This study demonstrated that induction chemotherapy does not improve overall survival and progression-free survival in patients with locally advanced squamous cell carcinoma of the head and neck receiving proton chemoradiotherapy.*

Keywords: *neoadjuvant therapy, tumors of the head and neck area, proton therapy.*

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BACKGROUND

Malignant tumors of the head and neck area represent a significant problem in modern oncology, for they take an important place within the structure of the morbidity and mortality of the population. According to the data from the Ministry of Health of the Russian Federation, in 2023, a total of 674,587 new cases of malignant neoplasms were registered, of which 25,038 cases were the tumors of the head and neck area [1].

Эффективность неоадъювантной химиотерапии перед протонной лучевой терапией опухолей головы и шеи

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АННОТАЦИЯ

Обоснование. *Злокачественные опухоли головы и шеи представляют собой значимую проблему в современной онкологии, так как занимают важное место в структуре заболеваемости и смертности населения. По данным Минздрава России, в 2023 году зарегистрировано 674 587 новых случаев злокачественных новообразований, из которых 25 038 составили опухоли головы и шеи.* ***Цель исследования*** *— оценить влияние индукционной лекарственной терапии на результаты лечения пациентов с местнораспространёнными опухолями головы и шеи, получивших лучевое лечение методом протонной терапии, методикой IMPT (протонная терапия с модулированной интенсивностью).* ***Методы.*** *Ретроспективное исследование включало анализ медицинских карт 103 пациентов с опухолями головы и шеи, которые были разделены на две группы: пациенты, получавшие индукционную химиотерапию с последующим проведением протонной химиолучевой терапии (n=50), и пациенты, не получавшие индукционного противоопухолевого лечения до начала протонной химиолучевой терапии (n=53). Для оценки различий между группами пациентов применяли t-тест для независимых выборок. Статистическая значимость различий считалась при уровне p <0,05.* ***Результаты.*** *Среднее время наблюдения за пациентами составило 15,7±7,8 месяца, медиана наблюдения — 13,4 месяца (IQR 11,6–21,6). В группе отслеженных пациентов ни один не прервал планового лечения, терапия завершена в установленный срок. В группе пациентов, получивших индукционную химиотерапию с последующим проведением протонной химиолучевой терапии, средняя общая выживаемость составила 27,65 месяца (95% ДИ 24,46–30,85), тогда как для группы пациентов, не получавших индукционного противоопухолевого лечения до начала протонной химиолучевой терапии, — 27,27 месяца (95% ДИ 22,15–31,72), что являлось статистически незначительным различием (Хи-квадрат 0,776; p=0,378). Оценка выживаемости без прогрессирования показала, что среднее время до прогрессирования в группе индукционной химиотерапии с последующим проведением протонной химиолучевой терапии составило 23,1 месяца (95% ДИ 19,6–26,6) против 21,2 (95% ДИ 16,7–25,7) в группе протонной химиолучевой терапии. Частота лейкопении I степени составила 30% в группе с индукционным химиотерапевтическим лечением против 20,8% в группе без индукционной химиотерапии, частота развития нарушений III степени — 26% и 11,3% соответственно, при этом осложнения III степени были отмечены только в группе пациентов, получавших индукционную химиотерапию (12%). Данные различия являются статистически значимыми (p <0,01).* ***Заключение.*** *Индукционная химиотерапия не улучшает общую выживаемость и выживаемость без прогрессирования у пациентов с местнораспространённым плоскоклеточным раком головы и шеи, получающих протонную химиолучевую терапию.*

Ключевые слова: *неоадъювантная терапия; опухоли головы и шеи; протонная лучевая терапия.*

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Among the modern therapeutic approaches, induction chemotherapy is used as a stage before the radical radiation therapy begins in cases when the volume of the tumor masses or their spreading do not allow providing the acceptable coverage by the exposure dosage or significantly increase the risks of serious complications in the normal tissues. The main objective of induction chemotherapy in that case is the decrease of the dimensions of the tumor masses and following the dosage-volume limitations when conducting the distant radiation therapy.

As of today, according to the MACH-NC meta-analysis that included the data from 107 research works with the participation of 19,805 patients, the application of induction chemotherapy has not demonstrated a significant improvement of the overall survival in patients (HR = 0.96; 95% CI: 0.90–1.01). At the same time, simultaneous chemoradiation therapy (CRT) has shown a more significant effect, decreasing the risk of mortality by 18% (HR = 0.82; 95% CI: 0.78–0.86). These results indicate the benefit of simultaneous chemoradiation therapy before induction chemotherapy in the improvement of the overall survival of the patients [2]

In the treatment of locally spreading processes, induction chemotherapy was repeatedly compared to the combined mode of chemoradiation therapy. No conclusive evidences were revealed in terms of improving the results, and the majority of research works devoted to the role of induction therapy in the treatment of tumors of the head and neck area, were evaluating specifically the photon beam therapy, while the role of proton therapy remains uninvestigated [3].

In the worldwide literature, there are data stating that proton irradiation suppresses the expression of factors, lympho-, angiogenesis and immune tolerance, facilitating the survival of less aggressive clones of tumor population, but their effects on the tumor biology remains poorly investigated [4, 5]. Because the efficiency of proton therapy is confirmed by our own clinical observations, there remains an interest to the improvement of long-term efficiency results by means of intensifying the anti-tumor medication therapy [6].

Research aim: The main aim of the research was to conduct a comparative analysis of two groups by key clinical outcomes, including the overall survival (OS) and progression-free survival (PFS), as well as to determine the effects of induction chemotherapy on the hematological toxicity.

METHODS

Research design

This retrospective research included an analysis of medical records from 103 patients with tumors in the head and neck area, which were divided into two groups: the patients receiving induction chemotherapy with further conduction of proton chemoradiation therapy (IPCRT) (n=50), and the patients not receiving induction antitumor therapy before the initiation of proton chemoradiation therapy (PCRT) (n=53).

For checking the conformity of the distribution of the quantitative variables to the normal one in each of the groups, the Shapiro-Wilk test was used. Despite the deviation from the normal distribution when evaluating the dosages of applied radiation therapy, taking into consideration the range of clinically recommended dosages, the analysis was carried out using the t-test for independent samples. Statistical significance of differences was considered in cases of p being < 0.05.

Conformity Criteria

The retrospective research was enlisting the patients with morphologically confirmed squamous cell cancer of the oropharynx or of the oral cavity, the locally spreading stage of the disease (III–IVb), the absence of signs of remote metastatic activity (M0), the absence of previously conducted radiation therapy and the satisfactory functional status — ECOG 0-1.

Research facilities and duration

From January 2019 until December 2024, proton beam therapy sessions were arranged with the use of ProteusPlus235 proton-cyclotron complex within the premises of the Federal State Budgetary Institution “Federal Scientific and Clinical Center of Medical Radiology and Oncology” under the Russian Federal Medical-Biological Agency in a total of 4,049 patients. The selection of patients was carried out using the “Protoregistr-2021” database, developed and registered within the framework of the state assignment from the Russian Federal Medical-Biological Agency [7].

Ethical review

All the research participants have signed the voluntary informed consent for treatment. The authors claim that the approval from the Ethics committee was not required, for the retrospectively analyzed data were based on the anonymized data and the treatment was conducted in accordance with the clinical recommendations from the Ministry of Health of the Russian Federation.

Medical procedure description

The patients were receiving a cycle of proton therapy following the mode of five-days fractioning with a single dosage (SD) of 2Gr to the total dosages (TD) of 50–60Gr applied to the zones of local-regional lymphatic collector and with the total dosage of 66–70Gr applied to the area of the primary tumor focus and the high risk zones. As an induction medication therapy, the patients were receiving the DCF scheme of not less than 2 cycles (Docetaxel-Cisplatin-Fluorouracil with a 21 days cycle) with further evaluation of the dynamic changes and, in the absence of signs of progression, with the conduction of proton chemoradiation therapy.

The dosimetric planning of proton therapy was carried out using the Phillips Pinnacle 3 planning system for the treatment conducted using the ProteusPlus235 apparatus with the Pencil Beam Scanning methods.

All the patient cases were discussed during the multi-disciplinary consilium, where decisions were made on the management tactics. The detailed characteristics are summarized in table 1. The test groups were comparable by the key clinical characteristics. A demonstration of the differences between proton and photon therapy plans in the dosimetric distribution is shown in Fig.1.

Statistical analysis

The median of follow-up was 13.4 months (IQR: 11.6–21.6 months). The mean follow-up time for the patients was 15.7±7.8 months. In the group of tracked patients, no one has interrupted the scheduled treatment, the therapy was completed at the pre-defined time. For the evaluation of the differences between the groups of patients, t-tests were used for independent samples. The statistical significance of differences was the p level being < 0.05.

Table 1

Comparative and quantitative characteristics of the test groups of patients

Parameter	IPCRT (n=50)	PCRT (n=53)	Comparability (p-value)
Gender, n (%)			
• M	36 (72)	35 (66)	0.513
• F	14 (28)	18 (34)	
Age (mean ± SD)	55.9±10.2	55.3±11.9	0.804
Tumor stage			
• 2	12	16	0.772
• 3	16	15	
• 4	22	22	
N-stage			
• 1	38	33	0.142
• 2	7	16	
• 3	5	4	
AJCC stage (TNM)			
• III	27 (54)	25 (52.1)	0.849
• IV	23 (46)	23 (47.9)	
Total focal dosage			
• High risk	66.2±2.1	65.8±2.4	0.761
• Mid risk	54.0±3.4	53.7±3.2	0.638
• Low risk	50.5±2.9	50.2±2.7	0.078
CRT type			
• Cisplatin	25 (50)	28 (52.8)	0.928
• Carboplatin	25 (50)	25 (47.2)	
Topographic group			
• The oropharynx	30 (60)	28 (52.8)	0.593
• The oral cavity	20 (40)	25 (47.2)	

Note. IPCRT — induction chemotherapy with further conduction of proton chemoradiation therapy, PCRT — proton chemoradiation therapy.

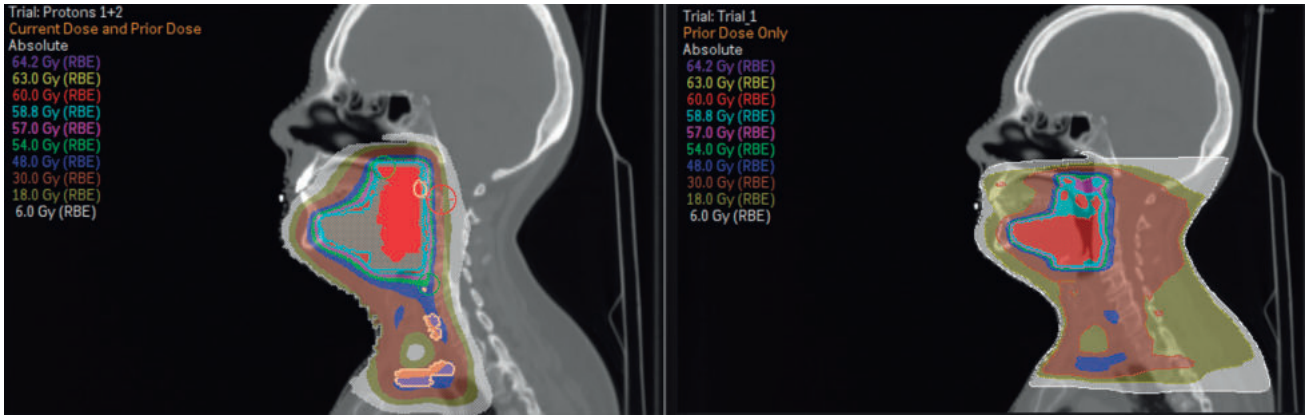

Fig. 1. Dosimetry differences in the plans of proton (on the left side) and photon (on the right side) radiation therapy.

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RESULTS

Research sample (participants) and primary findings

The first stage included the analysis of the parameters of overall survival in the test groups of patients using the Kaplan-Meier curves (Fig. 2). In the group of patients receiving induction chemotherapy, the mean OS was 27.65 months (95% CI: 24.46 – 30.85), while in the group without induction chemotherapy — 27.27 months (95% CI: 22.15–31.72), which was a statistically insignificant difference (Chi-square = 0.776, p=0.378). The median OS for both test groups was not achieved due to the limited duration of following-up the patients.

The evaluation of the progression-free survival rate has shown that the mean time to progression in the group of induction chemotherapy was 23.1 months (95% CI: 19.6–26.6), versus 21.2 months (95% CI: 16.7–25.7) in the group where the treatment did not include the induction. The median time to progression was the following: the group with the induction type of chemotherapy — 26.3 months (95% CI: 18.7– 33.8), the group without the induction mode — 18.8 months (95% CI: 8.0–29.6). Despite the fact that the median PFS was higher in the group with induction chemotherapy, no statistically significant differences were detected between the groups (Chi-square = 0.293, p=0.589) (Fig. 3).

None of the analyzed factors (stage of the disease, test group, HPV-status, age, type of the used antitumor medication) had a significant statistical effect on our patient sample.

Evaluations were also carried out for the rate and the degree of developing leucopenia: as expected, the group of induction medication therapy demonstrates the higher rate and degree of hematological abnormalities (table 2).

The rate of grade 1 leucopenia was 30% in a group of patients, receiving induction chemotherapy with further proton chemoradiation therapy, versus 20.8% in a group of patients not receiving induction antitumor therapy before the initiation of proton chemoradiation therapy, the rate of developing grade 3 disorders was 26% in the group of induction chemotherapy and 11.3% in the group without the induction, while grade 3 complications were reported only in the group of patients receiving induction chemotherapy (12%). These differences are statistically significant (p <0.01) and confirm that induction chemotherapy increases the rate and the degree of leucopenia severity.

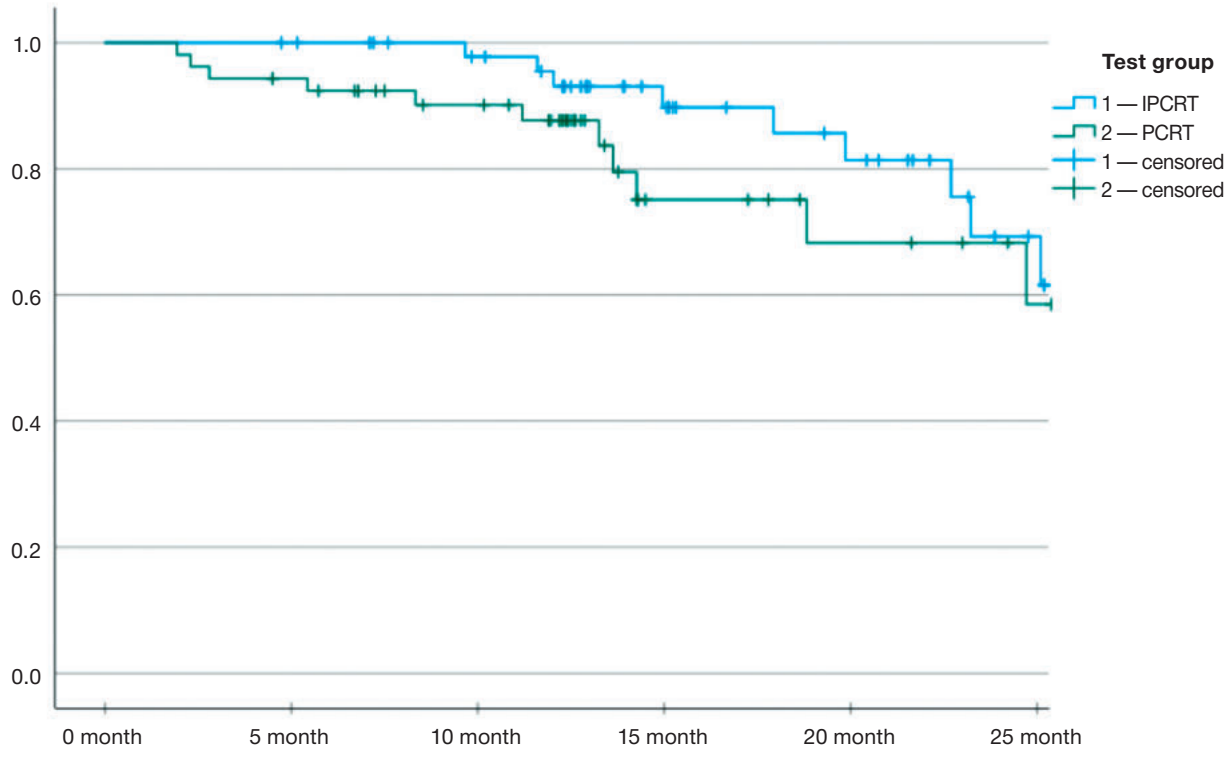

Fig. 2. Overall survival graph for the patients of the test groups using the Kaplan-Meier method. IPCRT — induction chemotherapy with further proton chemoradiation therapy; PCRT — proton chemoradiation therapy.

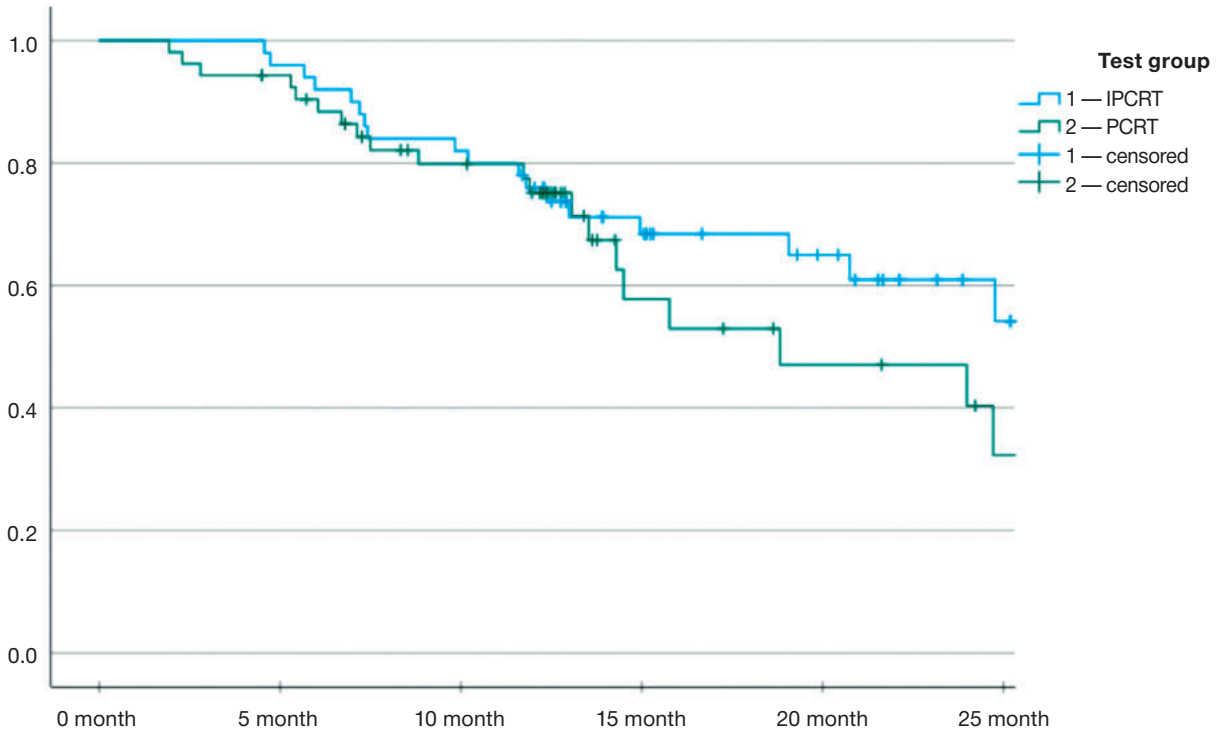

Fig. 3. Progression-free survival rate graph for the test groups — Kaplan-Meier's method. IPCRT — induction chemotherapy with further proton chemoradiation therapy; PCRT — proton chemoradiation therapy.

Table 2

Assessment of the degree of leucopenia development

Group	Leucopenia degree								Total, *n*
	0	%	1	%	2	%	3	%	
IPCRT	16	32.0	15	30.0	13	26.0	6	12.0	50
PCRT	36	67.9	11	20.8	6	11.3	0	0.0	53
Total	52	-	26	-	19	-	6	-	103

Note. IPCRT — induction chemotherapy with further proton chemoradiation therapy; PCRT — proton chemoradiation therapy.

DISCUSSION

Our research has demonstrated that induction chemotherapy does not improve overall survival and progression-free survival in patients with locally spreading squamous cell cancer of the head and neck area, receiving proton chemoradiation therapy. However, the presence of induction therapy is associated with the higher rate of hematological disorders, which evidently leads to interrupting the treatment, to the usage of additional resources, as well as to the elevation on the risks of complications. Thus, such an approach should not be used in the routine practice. These data confirm the tendency observed in the publications worldwide, now transferred to the group of proton therapy.

The research had a number of limitations, primarily, due to its relatively small sample size (n=103), which may limit the statistical power of analysis. Also, the follow-up period was lasting at an average of 15.7 months, which may be insufficient for the evaluation of long-term treatment effects.

CONCLUSION

The routine usage of induction chemotherapy before proton chemoradiation therapy does not provide significant benefits in terms of overall survival and progression-free survival rates. Additional factors, having a potential effect on the patients' survival rate and treatment tolerability, include the local toxicity, the volume of the tumor masses and the fractioning modes, which represent a subject for our further research.

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ADDITIONAL INFORMATION

Author contributions. *Yu.D. Udalov*: the concept and design of the study; *A.V. Nezvetsky*, *I.V. Nezvetskaya*: material processing, data analysis, writing and editing of the text. Thereby, all authors provided approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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REFERENCES

1. *Злокачественные новообразования в России в 2023 году (заболеваемость и смертность)* / под ред. А.Д. Каприна и др. Москва: МНИОИ им. П.А. Герцена — филиал ФГБУ «НМИЦ радиологии» Минздрава России, 2024. 276 с. [*Malignant neoplasms in Russia in 2023 (morbidity and mortality).* Ed. by A.D. Kaprin, et al. Moscow: P.A. Herzen Moscow Medical Research Institute — branch of the Federal State Budgetary Institution «NMITS of Radiology» of the Ministry of Health of Russia; 2024. 276 p. (In Russ.)]
2. Lacas B, Carmel A, Landais C, et al. MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 107 randomized trials and 19,805 patients, on behalf of MACH-NC Group. *Radiother Oncol.* 2021;156:281–293. doi: 10.1016/j.radonc.2021.01.013
3. Machiels JP, René Leemans C, Golusinski W, et al. EHNS Executive Board, ESMO Guidelines Committee, ESTRO Executive Board. Reprint of "Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up". *Oral Oncol.* 2021;113:105042. doi: 10.1016/j.oraloncology.2020.105042
4. Lupu-Plesu M, Claren A, Martial S, et al. Effects of proton versus photon irradiation on (lymph) angiogenic, inflammatory, proliferative and anti-tumor immune responses in head and neck squamous cell carcinoma. *Oncogenesis.* 2017;6(7):e354. doi: 10.1038/oncsis.2017.56
5. Huang D, Ding Y, Zhou M, et al. Interleukin-8 mediates resistance to antiangiogenic agent sunitinib in renal cell carcinoma. *Cancer Res.* 2010;70(3):1063–1071. doi: 10.1158/0008-5472.CAN-09-3965
6. Удалов Ю.Д., Незвецкий А.В., Данилова Л.А., и др. Анализ результатов протонной лучевой терапии пациентов с плоскоклеточным раком головы и шеи // *Онкологический журнал: лучевая диагностика, лучевая терапия*. 2022. Т. 5, № 3. С. 9–17. [Udalov YuD, Nezvetskiy AV, Danilova LA, et al. Analysis of the results of proton radiation therapy in patients with squamous cell carcinoma of the head and neck. *Journal of oncology: diagnostic radiology and radiotherapy*. 2022;5(3):9–17]. doi: 10.37174/2587-7593-2022-5-3-9-17 EDN: VFVJPL
7. Патент РФ № 2021620627/02.04.2021. Удалов Ю.Д., Крючко Д.С., Слобина Е.Л., и др. *База данных пациентов, получавших протонную терапию по поводу онкологических заболеваний в системе ФМБА России.* [Patent RUS № 2021620627/02.04.2021. Udalov YuD, Kryuchko DS, Slobina EL, et al. *Database of patients receiving proton therapy for oncological diseases in the FMBA system of Russia*. (In Russ.)] EDN: KGBDVF

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