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Long-term results of comprehensive treatment of patients with locally advanced tongue cancer using selective intraarterial and systemic polychemotherapy

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Abstract

Aim – to evaluate the long-term results of complex treatment of patients with locally advanced tongue cancer (T3-4N0-3M0) using modified selective intra-arterial polychemotherapy and systemic polychemotherapy.

Material and methods. Depending on the polychemotherapy regimen, taking into account the designated classifications, all patients were divided into two groups. The study group included 51 patients who received intra-arterial polychemotherapy according to the PF regimen, followed by radiation therapy. The control group included 50 patients who received intravenous polychemotherapy according to the PF regimen, followed by radiation therapy. With positive dynamics in the study group and the control group (partial tumor regression), surgical treatment was performed in the amount of hemiglossectomy. In case of complete tumor regression, the 2nd stage of the telegammatherapy course on the tongue was performed up to a total dose of 60 Gy. In case of oncological process stabilization, the 2nd stage of the telegammatherapy course on the tongue was performed up to a total dose of 60 Gy, followed by palliative courses of systemic polychemotherapy. In case of disease progression, palliative courses of systemic polychemotherapy were performed.

Results. Three-year survival in the study group was 80.1±6%, while in the control group it was 56.6±7% ($p<0.05$). Five-year survival among patients in the study group was 39.4±7%, while in the control group it was 2 times lower – 18.9±5% ($p<0.05$). About 7% of patients in the study group survived for more than 8 years.

Conclusions. The treatment regimen we developed for patients with locally advanced tongue cancer, which includes selective intra-arterial polychemotherapy followed by radiation therapy to the primary tumor and areas of regional metastasis, increased the median survival, three- and five-year survival.

Keywords: locally advanced tongue cancer, selective intra-arterial polychemotherapy, radiation therapy.

Conflict of Interest: nothing to disclose.

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Отдаленные результаты комплексного лечения больных с местнораспространенным раком языка с использованием селективной внутриартериальной и системной полихимиотерапии

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Аннотация

Цель – оценить отдаленные результаты комплексного лечения больных с местнораспространенным раком языка (Т3-4N0-3M0) с использованием модифицированной селективной внутриартериальной полихимиотерапии и системной полихимиотерапии.

Материал и методы. В зависимости от режима проведения полихимиотерапии с учетом обозначенных классификаций все пациенты были распределены на две группы. В исследуемую группу вошли пациенты (51 человек), которые получили внутриартериальную полихимиотерапию по схеме PF с последующим проведением лучевой терапии. В контрольную группу вошли пациенты (50 человек), которые получили внутривенную полихимиотерапию по схеме PF с последующим проведением лучевой терапии. При положительной динамике в группах (частичная регрессия опухоли) выполняли оперативное лечение в объеме гемиглоссэктомии. При полной регрессии опухоли проводили второй этап курса телегаммотерапии на язык до СОД – 60 Гр. При стабилизации онкологического процесса проводили второй этап курса телегаммотерапии на язык до СОД – 60 Гр, а после – паллиативные курсы системной полихимиотерапии. При прогрессии заболевания – паллиативные курсы системной полихимиотерапии.

Результаты. Трехлетняя выживаемость в исследуемой группе равна 80,1±6%, а в контрольной группе – 56,6±7% (p<0,05). Пятилетняя выживаемость среди пациентов исследуемой группы – 39,4±7%, а в контрольной группе в два раза ниже – 18,9±5% (p<0,05). Около 7% больных в исследуемой группе прожили более 8 лет.

Заключение. Разработанная нами схема лечения больных с местнораспространенным раком языка, которая включает проведение селективной внутриартериальной полихимиотерапии с последующей лучевой терапией на первичную опухоль и зоны регионарного метастазирования, позволила увеличить медиану выживаемости, трех- и пятилетнюю выживаемость.

Ключевые слова: местнораспространенный рак языка, селективная внутриартериальная полихимиотерапии, лучевая терапия.

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Список сокращений
ОГШ – опухоли головы и шеи; ЗНО – злокачественное новообразование; РПР – рак полости рта; СОД – суммарная очаговая доза; РОД – разовая очаговая доза.

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INTRODUCTION

Carcinomas of the head and the neck make up a substantial group of the entire oncopathology, an 18-20% group of malignant tumors characterized with a progressing morbidity [1].

Following the national and worldwide statistics, cancer of the oral organs and the oropharyngeal cavity accounts for 2% to 10% of all human malignant tumors and for up to 15-20% among head and neck tumors. The incidence rate of cancer of the oral organs in Russia in 2013 was 24.4 per 100 thousand people, whereas in 2023, 31.9 per 100 thousand people. The amount of patients with malignant tumors of the oral cavity under regular check-up in the cancer care facilities was 48.2% in 2013, whereas in the year 2023 it was 53.9%. The proportion of malignant tumors of the oral cavity identified in the advanced stages (Stage III-IV) in 2013 in Russia was 28.4%, and in 2023, it was 39.5%. The mortality rate in patients with this pathology in the course of one year after the diagnosis in Russia was 35.0% in 2013 vs. 27.0% in 2023 [2].

The cancer of the tongue and of the oral cavity, according to many authors, ranks first among other malignant tumors of the oral mucosa [3]. Whereas in the year 2011 in Russia, 7674 cases of primary diagnoses of tongue cancer were identified, in the year 2023 the occurrence reached 8681 cases including 25.6% cases in stage III, and 39.5% cases with stage IV [1]. In the USA, the number of patients with identified oral cavity cancer was 47010, making it 1.2% of all malignant neoplasms. Oral cavity and pharynx cancer most often occurs in men aged 55–64 years, with a five-year survival rate of 63.2% [4].

In the treatment of locally advanced cancer of the oral cavity, the combined method prevails that brings together surgical intervention and radiation therapy in various combinations. [5].

Oral cavity cancer is characterized with high mortality rates. This is accounted for by the low disease identification rate at early stages, highly malignant progression of the disease, fast expansion of the tumor process to nearby vital organs, frequent metastases to regional lymph nodes, high resistance to chemo- and radiotherapy, and limited availability of contemporary molecular and biological methods of examination and treatment in some clinics [6]. Specific tumor markers of the oral cavity cancer (SCC, S100A8, IL-6, IL-8, KI-67, Gli1, etc.) in the patient's saliva, blood serum, and tumor biopsy material may be instrumental in choosing the treatment methods [7, 8].

Radiotherapy is considered the main method of treatment of patients with oral cavity cancer. Regretfully, the efficiency of radiotherapy alone is not satisfactory: relapses and metastasis develop in 60-70% of observations, thus limiting the 5-year survival to 15-20%. Therefore, in order to improve efficiency of radiotherapy new regimens are developed; and some authors insist on increasing the exposure dose to 70 Gy [9].

Some research has focused on augmentation of effects of exposure by radiation-induced hyperthermia and magnetothermia, induction chemotherapy, and performance of simultaneous chemoradiotherapy [10–12].

Combination of intra-arterial multidrug chemotherapy using the Seldinger technique and retrograde superselective intra-arterial multidrug chemotherapy using the PF regimen with the radiotherapy has played a highly important role in the treatment of locally advanced squamous-cell carcinoma of the oral cavity: it resulted in the reduction of the malignant

Study Group	Control Group
2 neoadjuvant courses using modified PF regimen: - Cisplatin, 10 mg/m2, continuous 6-hour intra-arterial infusion: 10 days; - Fluoruracil, 250 mg/m2, continuous 6-hour intra-arterial infusion: 10 days. Interval between courses: 21 days. 21 days after two courses of intra-arterial polychemotherapy, irradiation of the primary tumor and regional metastasis zones was performed using the "Rokus" and "Agat" gamma-therapy units in the classical dose fractionation mode to the tongue - SBD - 2 Gy, TBD - 40 Gy, to the submandibular, cervical, supraclavicular regions on both sides - SBD - 2 Gy, TBD - 40 Gy per single stage.	**2 neoadjuvant courses of systemic multidrug chemotherapy using modified PF regimen:** - Cisplatin, 100 mg/m2, intravenous drip-feed: 1 day; - Fluoruracil, 1000 mg/m2, intravenous drip-feed, continuous 96-hour infusion: days 1-4. Interval between courses: 21 days. 21 days after two courses of systemic multidrug chemotherapy, irradiation of the primary tumor and regional metastasis zones was performed using the "Rokus" and "Agat" gamma-therapy units in the classical dose fractionation mode to the tongue - SBD - 2 Gy, TBD - 40 Gy, to the submandibular, cervical, supraclavicular regions on both sides - SBD - 2 Gy, TBD - 40 Gy per single stage.

Table 1. *Scheme of complex treatment of patients in the control and study groups*
Таблица 1. *Схема комплексного лечения больных в контрольной и исследуемой группах*

tumor of the oral cavity, and had the least number of side effects [13, 14].

AIM

To evaluate the long-term results of complex treatment of patients with locally advanced tongue cancer (T3-4N0-3M0) using modified selective intra-arterial polychemotherapy and systemic polychemotherapy.

MATERIAL AND METHODS

Case histories and outpatient cards of 323 patients with tongue cancer were studied. They had been treated at the G.V. Bondar Republican Cancer Center from 1995 to 2018. We excluded patients with intolerance to chemotherapeutic drugs, HIV infection, hepatitis B and C; clinically relevant cardiovascular disease, pregnancy or lactation, gastric or duodenal ulcer in the acute phase, diabetes mellitus. Thus, the retrospective controlled study included 101 patients.

In determining the stage of the disease, we adhered to AJCC-TNM Classification of Malignant Tumors, 8th Edition (American Joint Committee on Cancer) (2017).

Depending on the regimen of the multidrug chemotherapy and with regard to the said classifications, the patients were divided into two groups.

The study group included patients (51 persons) who had received intra-arterial polychemotherapy under the PF regimen with subsequent radiotherapy.

The control group included patients (50 persons) who had received intravenous polychemotherapy under the PF regimen with subsequent radiotherapy. The groups were comparable in the sex, age, and stage of the tumor process.

The scheme of complex treatment of patients in the control and the study groups follows in **Table 1**.

In cases of positive changes in the groups (partial regression of the tumor), surgical treatment was performed (hemiglossectomy). In cases of complete regression of the tumor, the second stage of gamma-ray therapy was performed to the tongue up to TBD=60 Gy. In cases of stabilization of the tumor process, the second stage of gamma-ray therapy was performed to the tongue up to TBD=60 Gy followed by palliative curses of systemic polychemotherapy. In cases of disease progression, palliative curses of systemic polychemotherapy were performed.

The statistical analysis of the obtained research results and indicators of remote effectiveness of treatment using the proposed methods of complex therapy for locally advanced tongue cancer was carried out in the Statistica 10 software suite.

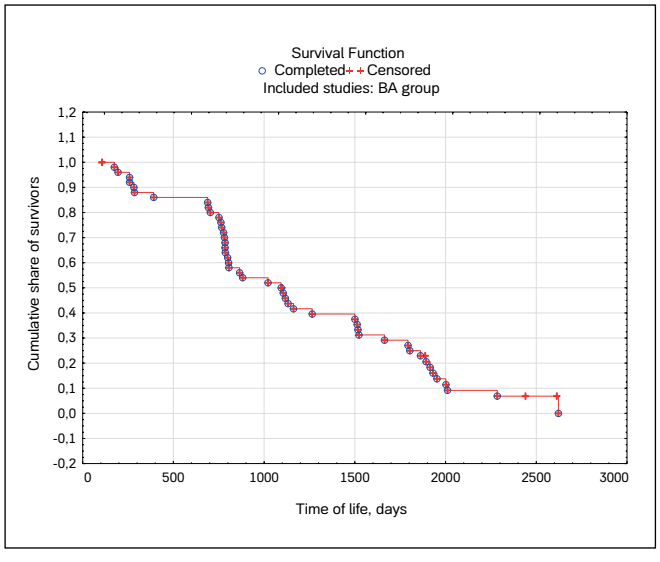

Figure 1. *Estimation of the survival function in the study group using the Kaplan-Meier maximum likelihood method.*
Рисунок 1. *Оценка функции выживаемости в исследуемой группе методом максимального правдоподобия Каплана – Майера.*

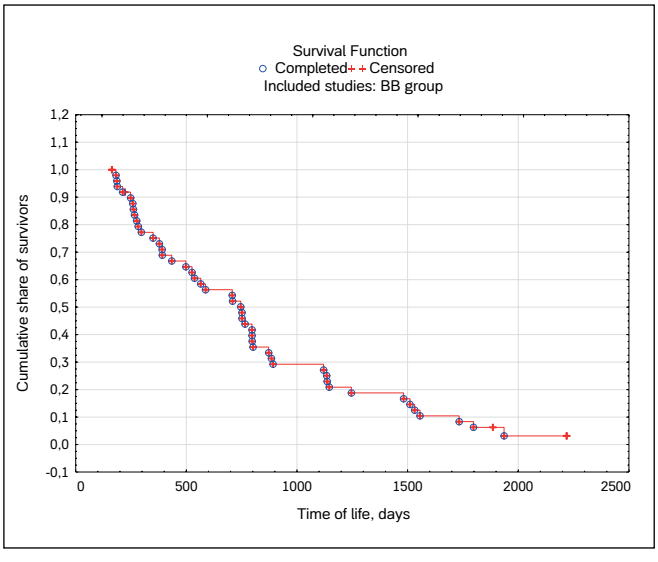

Figure 2. *Estimation of the survival function in the control group using the Kaplan-Meier maximum likelihood method.*
Рисунок 2. *Оценка функции выживаемости в контрольной группе методом максимального правдоподобия Каплана – Майера.*

Interval	Initial number	Proportion of diseased	Proportion of survivors	Total proportion of survivors	Relative risk	Median t_survival
1 year	51	11.9	88.1	100.0	0.03	1076
2 year	44	9.1	90.9	88.1	0.02	844
3 year	40	43.0	56.96	80.1	0.2	710
4 year	22	13.6	86.4	45.6	0.04	749
5 year	19	42.1	57.9	39.4	0.1	464
6 year	11	57.1	42.9	22.8	0.2	328
7 year	4	33.3	66.7	9.8	0.1	375
8 year	1	50.0	50.0	6.5		

Table 2. *Table of patient survival in the study group*
Таблица 2. *Таблица дожития пациентов в исследуемой группе*

Interval	Initial number	Proportion of diseased	Proportion of survivors	Total proportion of survivors	Relative risk	Median t_survival
1 year	50	22.5	77.6	100.0	0.1	711
2 year	37	27.0	72.97	77.6	0.1	524
3 year	27	48.2	51.9	56.6	0.2	349
4 year	14	35.7	64.3	29.3	0.1	476
5 year	9	44.4	55.6	18.9	0.2	388
6 year	5	44.4	55.6	10.5	0.2	380
7 year	2	50.0	50.0	5.8	0.2	159
8 year	1	100.0	0.0	2.9		

Table 3. *Table of patient survival in the control group*
Таблица 3. *Таблица дожития пациентов в контрольной группе*

For qualitative indicators, incidence rate was calculated (P, in %). In all cases, the discrepancies were deemed statistically significant at $p<0.05$.

In the calculation of survival and average life expectancy, the survival curve method was used. For a more detailed analysis of the degree of difference in survival curves, several tests were used: log-rank, Gehan-Wilcoxon, Cox, Cox-Mentel, Wilcoxon-Peto.

RESULTS

The specific feature of survival analysis is the presence of subjects who did not experience the event of interest during the study (death).

The time of life may be described mathematically by the survival function and the risk function. The survival function (St) characterizes the percentage of individuals surviving for more than t units of time, where t is measured from the start of the therapy (**Fig. 1, 2**).

Difference assessment test	Test assessment	Level of statistical significance (p=)
Gehan-Wilcoxon	-2.96	0.003
Cox F-test	1.55	0.018
Cox-Mentel	-2.91	0.004
Wilcoxon-Peto	2.96	0.003
Log-rank	2.77	0.006

Table 4. *Criteria for assessing the similarity of survival curves*
Таблица 4. *Критерии оценки одинаковости кривых выживаемости*

Comparing the amount of survivors in the two groups from the moment of the start of the therapy, the following conclusions can be made. On the 500th day from the start of treatment the proportion of survivors was 86±5%, and in the control group, 65±6% ($p<0.05$). On the 1000th day from the start of treatment, the proportion of survivors in the study group was 55±7%, and in the control group, 30±6% ($p<0.05$). On the 1500th day from the start of treatment, the proportion of survivors in the study group was 40±7%, and in the control group, 18±5% ($p<0.05$). On the 2000th day from the start of treatment, the proportion of survivors in the study group was 11±5%, and in the control group, 4±3% ($p>0.05$). On the 2500th day from the start of treatment, the proportion of survivors in the study group was 8±4%, and there were no survivors in the control group. Therefore, in all periods from the start of the treatment, the proportion of survivors in the study group was significantly higher than that in the control group; on the 1500th day it was more than 2.2 times higher ($t=2.6$, $p<0.05$).

To evaluate the survival of patients, tables of patient survival were calculated (**Tables 2, 3**).

It is seen from the tables, the cumulative proportions of survivors in the study group in all time intervals are higher than those in the control group of patients. Three-year survival in the study group was 80.1±6%, and in the control group, 56.6±7% ($p<0.05$). Five-year survival among patients in the study group was 39.4±7%, and in the control group it was twice as low: 18.9±5% ($p<0.05$). Eight-year survival in the study group is also two times higher than that in the control group, 6.5% vs. 2.9±2% ($p>0.05$). The median survival in the study group in practically all time intervals is higher than that in the control group. In the first year, median survival in the study group was 36 months vs. 23.7 months in the study group. In the second year, median survival in the study group was 28.1 months vs. 17.5 months in the control group. In the third year, median survival in the study

group was 23.7 months vs. 11.6 months in the control group. In the fourth year, median survival in the study group was 25 months vs. 15.9 months in the control group. In the fifth year, median survival in the study group was 15.5 months vs. 12.9 months in the control group. In the sixth year, median survival in the study group was 10.9 months vs. 12.6 months in the control group. In the seventh year, 12.5 months vs. 5.3 months in the control group. It is seen that the median survival in the sixth year in the study group was lower than that in the control group. Following the table data it is seen that the median survival was decreasing every year in both groups, but it increased in both groups in the fourth year.

The median survival in the study group was reached for 36.5 months, whereas in the control group it was only 24.9 months.

It is seen from **Table 4** that all known non-parametric tests of assessing the similarity of survival curves have high levels of statistical significance ($p<0.05$), therefore, survival curves are not similar in the two groups: in the study group, survival was higher than in the control group.

CONCLUSION

The median survival in the study group is 36.5 months and it is 24.9 months in the control group. Cumulative proportions of survivors in the study group in all time intervals are higher than those in the control group. Three-year survival in the study group is 80.1±6%, and it is 56.6±7% in the control group ($p<0.05$). Five-year survival among the patients of the study group is 39.4±7%, and in the control group it is twice as low: 18.9±5% ($p<0.05$). About 7% of patients in the study group survived for over 8 years.

The regimen of treatment of patients with locally advanced tongue cancer developed by us included selective intra-arterial multidrug chemotherapy with subsequent radiotherapy to the primary tumor and zones of regional metastasis. It increased the median survival, three- and five-year survival.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ	ADDITIONAL INFORMATION
Источник финансирования. Работа выполнена по инициативе авторов без привлечения финансирования.	***Study funding.*** The study was the authors' initiative without external funding.
Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.	***Conflict of interest.*** The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.
Участие авторов. Седаков И.Е. – сбор научного материала, редактирование статьи. Ползиков Г.Н. – формулировка цели исследования, оформление дизайна исследования, распределение пациентов в исследуемую и контрольную группы. Коктышев И.В. – расчет статистических показателей, анализ выживаемости больных в исследуемой и контрольной группе. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.	***Contribution of individual authors.*** Sedakov I.E.: collection of scientific material, editing of the article. Polzikov G.N.: formulation of the study objective, design of the study, distribution of patients into the study and control groups. Koktyshev I.V.: calculation of statistical indicators, analysis of survival of patients in the study and control groups. The authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.

ЛИТЕРАТУРА / REFERENCES

1. Nomura M, Fuwa N, Ito S, et al. Initial Experience of Intra-Arterial Chemotherapy Using a Novel External Carotid Arterial Sheath System Combined with Radiotherapy and Systemic Chemotherapy for Locally Advanced Tongue Cancer. Cancers (Basel). 2022;14(22):5529. DOI: 10.3390/cancers14225529

2. Kaprin AD, Starinsky VV, Shakhzadova AO. State of oncological care for the population of Russia in 2023. M., 2024:10-31. (In Russ.). [Каприн А.Д., Старинский В.В., Шахзадова А.О. Состояние онкологической помощи населению России в 2023 году. М.,2024:10-31].

3. Hussein AA, Helder MN, de Visscher JG, et al. Global incidence of oral and oropharynx cancer in patients younger than 45 years versus older patients: A systematic review. Eur J Cancer. 2017;82:115-127. DOI: 10.1016/j.ejca.2017.05.026

4. *Sarode G, Maniyar N, Sarode SC, et al. Epidemiologic aspects of oral cancer. Dis Mon. 2020;66(12):100988.* DOI: 10.1016/j.disamonth.2020.100988

5. Baba A, Hashimoto K, Kayama R, et al. Radiological approach for the newly incorporated T staging factor, depth of invasion (DOI), of the oral tongue cancer in the 8th edition of American Joint Committee on Cancer (AJCC) staging manual: assessment of the necessity for elective neck dissection. Jpn J Radiol. 2020;38(9):821-832. DOI: 10.1007/s11604-020-00982-w

6. Huang CC, Yang TL, Tseng WH, et al. An alternative surgical technique for advanced tongue/tongue base cancer without free flap reconstruction. J Formos Med Assoc. 2022;121(12):2626-2632. DOI: 10.1016/j.jfma.2022.07.007

7. Keshava A, Gugwad S, Baad R, Patel R. Gingival squamous cell carcinoma mimicking as a desquamative lesion. J Indian Soc Periodontol. 2016;20:75-78. DOI: 10.4103/0972-124X.164765

8. Siu A, Landon K, Ramos D. Differential diagnosis and management of oralulcers. Semin Cutan Med Surg. 2015;34:171-177. DOI: 10.12788/j.sder.2015.0170

9. Sokolovska MV. The effectiveness of tumor radiosensitization with low doses of ionizing radiation in radiation treatment of stage II–III oral mucosa cancer. Ukrainian Journal of Radiology. 2015;23(2):151-153. (In Ukrainian). [Соколовська М.В. Ефективність радіосенсибілізації пухлини малими дозами іонізуюч ого випромінення при променевомулікуванні раку слизової оболонки ротової порожнини II–III стадій. Український радіологічний журнал. 2015;23(2):151-153].

10. Sher DJ, Yan J, Day A, et al. Comparative effectiveness of primary radiotherapy versus surgery in elderly patients with locally advanced oropharyngeal squamous cell carcinoma. Oral Oncol. 2019;88:18-26. DOI: 10.1016/j.oraloncology.2018.11.004

11. Lim SH, Sun JM, Hong J, et al. Induction chemotherapy followed by concurrent chemoradiotherapy versus CCRT for locally advanced hypopharynx and base of tongue cancer. Korean J Intern Med. 2021;36(1):217-224. DOI: 10.3904/kjim.2019.161

12. Harsh KK, Maharia SR, Nirban RK, et al. Metronomic palliative chemotherapy in locally advanced, recurrent and metastatic head-and-neck cancer: A single-arm, retrospective study of a regional cancer center of North India (Asia). J Cancer Res Ther. 2020;16(3):559-564. DOI: 10.4103/jcrt.JCRT_702_18

13. Takayama K, Nakamura T, Takada A. Treatment results of alternating chemoradiotherapy followed by proton beam therapy boost combined with intra-arterial infusion chemotherapy for stage III-IVB tongue cancer. J Cancer Res Clin Oncol. 2016;142(3):659-67. DOI: 10.1007/s00432-015-2069-0

14. Engibaryan MA, Gvaramiya AK. An innovative approach to the treatment of locally advanced tongue cancer. Modern problems of science and education. 2021;1. [Енгибарян М.А., Гварамия А.К. Инновационный подход к лечению местнораспространенного рака языка. Современные проблемы науки и образования. 2021;1]. DOI: 10.17513/spno.30399