

**RESULTS OF TREATMENT OF NON-EPITHELIAL MALIGNANT TUMORS OF THE  
MAXILLOFACIAL REGION****Dr. Khasanov Ak. I.\*<sup>1</sup>, Bekmirzaev R. M.<sup>1</sup>, Primkulov B. K.<sup>2</sup>, Khasanov Ad. I.<sup>3</sup>, Shukurov Z. I.<sup>1</sup>, Kaxarov A. D.<sup>3</sup>,  
Nishonboev L. S.<sup>1</sup>**<sup>1</sup>Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology – RSPMCO.<sup>2</sup>R Fergana branch of RSPMCO.<sup>3</sup>R Tashkent State Dental Institute.**\*Corresponding Author: Dr. Khasanov Ak. I.**

Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology – RSPMCO.

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**ABSTRACT**

The scientific research is aimed at improving the results of treatment of patients with non-epithelial malignant tumors of the maxillofacial region by improving intra-arterial chemotherapy and using reconstructive reconstructive operations using titanium plates in 117 patients treated in the department of head and neck tumors of the *RSPMCO* and *R* of the Ministry of Health of the Republic of Uzbekistan. Osteosarcoma was most common morphologically in 34 (29%) patients. In patients who received intra-arterial chemotherapy, immediate and long-term treatment results are much better than in patients who received traditional methods of treatment.

**KEYWORDS:** non-epithelial malignant tumors of the maxillofacial region, intra-arterial chemotherapy, reconstruction using titanium plates.

**INTRODUCTION**

Treatment of malignant non-epithelial tumors of the maxillofacial region presents a complex and urgent problem of modern clinical oncology due to a long asymptomatic course and significant difficulties in diagnosis. In this connection, many patients (70-90%) turn to an oncologist with locally advanced stages of the disease.<sup>[1,2]</sup>

In malignant non-epithelial tumors of these localizations, when several anatomical departments are involved in the tumor process, resection of the maxillofacial region leads to violations of the functions of chewing, swallowing, speech, cosmetic defects.<sup>[3,4]</sup> In surgical treatment of malignant neoplasms of the maxillofacial region, which is in close anatomical connection with the orbital region and grows into it, in 25-60% of patients.<sup>[4,5]</sup>

Sarcomas of the head and neck are similar to sarcomas of other parts of the body, however, due to their location, proximity of the orbit, brain and cranial nerves, radical operations are complicated, which in turn increases the likelihood of tumor recurrence.<sup>[6]</sup>

Due to the emergence of new chemotherapy drugs and also the development of various schemes, methods of their administration, it is often possible to translate an unresectable tumor process into a resectable one.<sup>[7,8]</sup>

The use of intra-arterial regional chemotherapy, which provides the introduction of drugs into an arterial vessel that supplies blood to the tumor location area, is relevant, in which the tumor is damaged as much as possible, with minimal damage to various organs and body systems with chemotherapy.<sup>[9,10,11,12]</sup> For tumors of the head and neck, the most effective method of regional chemotherapy is intra-arterial chemotherapy, carried out by catheterization of the external carotid artery or its branches.<sup>[8,13]</sup>

To improve antitumor therapy, hyperthermia occupies a special place as a modifier, and the combination of the latter with chemotherapy or radiation therapy leads to an increase in 5-year survival rates. The possibility of treating sarcomas with intra-arterial chemotherapy in combination with modifiers needs special research.

Restoration of the bone integrity of the mandible after removal of the tumor is the most urgent problem of modern oncology and maxillofacial surgery. The leading role in reconstructive surgery of the facial skeleton is occupied by bone-plastic surgery for defects of the lower jaw. The consequences of surgical interventions for tumors of the mandible cause significant impairment of the function of the mandible and disfigurement of the soft tissues of the lower facial area.<sup>[14,15,16]</sup>

Based on this, the purpose of surgical intervention on the lower jaw is not only to radically remove the tumor, but also to simultaneously restore the continuity of the mandibular arch to prevent possible functional and cosmetic disorders.<sup>[17,18]</sup>

**The purpose of the study.** Improving the results of treatment of patients with non-epithelial malignant tumors of the maxillofacial region by improving intra-arterial chemotherapy and using reconstructive reconstructive operations using titanium plates.

## MATERIALS AND METHODS

The results of treatment of 117 patients with malignant non-epithelial tumors of the maxillofacial region who

were treated in the department of head and neck tumors of the RSPMCO and R of the Ministry of Health of the Republic of Uzbekistan in the period from 2000 to 2018 were analyzed. There were 72 men (61.5%), 45 women (38.5%). The age of the patients ranged from 18 to 75 years. The average age of the patients was  $39.1 \pm 1.5$  years. All 117 patients, depending on the method of treatment, were divided into 4 groups, 72 patients were operated on, and the rest did not undergo surgery for various reasons. (Table 1).

**Table 1: Distribution of patients by groups and depending on the treatment regimen.**

Group	Number of patients	The treatment regimen	Operated
1	20 (17%)	Long-term intra-arterial polychemotherapy with local UHF hyperthermia + radiation therapy followed by surgery	13
2	27 (23%)	Long-term intra-arterial polychemotherapy + radiation therapy followed by surgery	15
3 control	52 (44,5%)	Systemic intravenous polychemotherapy + radiation therapy followed by surgery	29
4-я control	18 (15,5%)	Radiation therapy followed by surgery	15
Total		117	72

According to the clinical classification and classification system TNM (2010) (AJSS), in our study T1a and T1b accounted for 29 (24.8%) patients, and tumors with T2a and T2b stage - 88 (75.2%) patients. (Table 2).

Metastases to the regional lymph nodes of the neck were noted in 25 (21.3%) patients. Distant metastases – in 9 (7.6%).

**Table 2: Distribution of the tumor process by TNM.**

№	Stage by TNM	Number of patients	Metastases to regional l/n	Distant metastases
1	T1a	15(12,8%)	3	
2	T1b	14(11,9%)	2	1
3	T2a	17(14,5%)	2	2
4	T2b	71(60,6%)	18	6
	Total	117(100%)	25(21,3%)	9(7,6%)

In our study, we also studied the degree of differentiation of tumor cells. Highly differentiated tumors ("G1- G2" - 59.7%) were more common than low-differentiated ("G3- G4" - 40.3%).

The predominance of the T2b process in patients of the 1st 16 (80%) and 2nd groups - 21 (77.7%) attracts attention. In the 3rd and 4th groups, respectively 42.3% and 66.6%. Metastatic lesion of regional lymph nodes was most common in groups 1 and 2.

The study showed that in 68 patients (58.1%), the primary tumor was most often localized in the upper jaw, in the lower jaw in 22 (18.8%), in the nasal cavity in 12 (10.2%), in the lattice labyrinth in 6 (5.1%), soft tissue tumors of the facial part in 7 (5.9%) patients. They were

less common in the thickness of the tongue, which was observed in 2 (1.7%) patients. (Table 3). On the side of the lesion, the presence of a primary tumor of the maxillofacial region was found on the right in 56 (47.8%) patients, on the left 52 (44.5%) and in the middle of the face in 9 (7.7%).

When studying the morphological characteristics of tumors, it was revealed that osteosarcoma was most often diagnosed in 34 (29%) cases, fibrosarcoma was the second most common in 23 (19.6%) patients, reticulosarcoma, epithelioid sarcoma and Ewing's sarcoma were less common in 1 (0.85%) cases. Such frequent diagnosis of osteosarcoma, up to 30.4%, was also observed in the works of Batoul Alishahi (2015).<sup>[19]</sup>

We used the following scheme for intra-arterial polychemotherapy: doxorubicin 15 mg/m<sup>2</sup>, intra-arterial for 6-8 hours 1.6 days at a total dose of 60-80 mg; cisplatin 15 mg/m<sup>2</sup> intra-arterial for 6-8 hours with

hyperhydration 2,3,4,5 days at a total dose of 100 mg, as well as Cyclofosfan 400 mg/m<sup>2</sup> 1.6 days in total a dose of 1000-1200 mg, intramuscularly only.

**Table 3: Distribution of patients by histological structure and initial localization of the tumor.**

№	Histological structure of the tumor	Number of patients	Percentage of the total number of observations	Nasal cavity	Lattice labyrinth	Lower jaw	Upper jaw	Soft tissue tumors of the facial part	Tumors of the tongue
1	Osteosarcoma	34	29		2	7	25		
2	Fibrosarcoma	23	19,6	1	1	2	17	2	
3	Angiosarcoma	12	10,2	1		4	5	1	1
4	Esthesioneuroblastoma	9	7,6	8	1				
5	Neurogenic sarcoma	8	6,8		1	3	3	1	
6	Rhabdomyosarcoma	8	6,8				6	1	1
7	Chondrosarcoma	6	5,1	1		4	1		
8	Fibrous histiocytoma	6	5,1		1		5		
9	Odontogenic sarcoma	2	1,7				2		
10	Mesenchymal sarcoma	2	1,7					2	
11	Epithelioid sarcoma	1	0,85				1		
12	Reticulosarcoma	1	0,85			1			
13	Unclassified sarcoma	2	1,7				2		
14	Mixosarcoma	2	1,7	1			1		
15	Ewing 's sarcoma	1	0,85			1			
16	Total	<b>117</b>	<b>100</b>	<b>12</b>	<b>6</b>	<b>22</b>	<b>68</b>	<b>7</b>	<b>2</b>

Teratron (Canada) and Agat-S (Russia) devices were used for remote telegammothery. Radiation therapy was performed from 2 oncoming fields, mainly in the GENUS 3 Gray per day, 5 times a week, SOD 40 Gray. 3 weeks after the end of neoadjuvant chemoradiotherapy in various variants, the patients underwent surgical intervention.

Out of 22 patients with mandibular tumor, 5 patients had new titanium plates developed by us installed after removal of the tumor from the mandible.

The effectiveness of treatment was assessed by: 1) the clinical effect according to the recommendations of the WHO Committee of Experts, 2) the degree of toxicity of chemotherapy on the scale of Toxicity Criterion NCIC, 3) the general condition of the patient (Performance status) on the Karnovsky scale (activity, %) and the WHO ECOG on the point system.

Pathomorphosis was classified according to 4 degrees of damage in accordance with the criteria.

We have created an electronic codifier based on the data obtained in the Microsoft Office Excel (2003) program,

which includes 131 features, in each feature from 2 to 10 gradations.

The obtained results were statistically processed using the Student-Fisher method. The long-term results of treatment according to the survival criterion were evaluated by the method of plotting the survival schedule according to KaplanE.L. and Meier R. (1958), version SPSS-16 for Windows (2007). At the same time, the overall and relapse-free 3-year and 5-year survival rates were calculated depending on the treatment tactics at the first stage of treatment. The differences were considered significant at  $P < 0.05$ .

## RESULTS OF TREATMENT

When studying the results of treatment of the 4th group of patients who received traditional methods of treatment with non-epithelial malignant tumors of the maxillofacial region, it was shown that 18 patients received combined treatment, including 40 Gray SOD telegammothery and subsequent surgery after 3-4 weeks. At stage 1, during receiving preoperative radiation therapy, the single dose was different. 3 patients from this group received radiation therapy at their place of residence, and

they were admitted to RSNPMTSOIR for surgical treatment. Therefore, it was not possible to determine the immediate results of radiation therapy in these patients.

Surgical intervention, as the second stage of combined treatment, was used in 15 (83.3%) patients who sought medical help.

Overall 3- and 5-year survival rates were calculated depending on the treatment tactics at the first stage. In group 4, 15 out of 18 patients received combined treatment (radiation therapy + surgery), and the remaining 3 patients received only radiation therapy.

The results of treatment in patients receiving combined treatment were calculated by Kaplan E.L. and Meier R. (1958). The overall 3-year cumulative survival rate was  $47.1 \pm 3.3\%$ , and the 5-year cumulative survival rate was  $33.3 \pm 4.8\%$ . At the same time, 3-year relapse-free cumulative survival was  $25.3 \pm 4.9\%$ , 5-year -  $13.3 \pm 5.7\%$ .

Of the 15 patients who received combined treatment, 86.7% of patients had a recurrence of the tumor. When studying the overall survival rate in patients who received only radiation therapy, it was shown that no one overcame the 5-year period.

Thus, in the 4th group of patients, the 3- and 5-year survival rates were low, especially if the patient received only radiation therapy.

**In group 3**, 52 patients received systemic chemotherapy and radiation therapy. At the same time, the patients received preoperative radiation therapy mainly by ROD 3 Gray 5 times a week, SOD 40 Gray.

When studying the toxic effect of chemoradiotherapy by the criterion of Somatotoxicity Criterion - NCIC, hematological toxicity was detected in all (41) patients, and in the remaining 11 patients, toxicity could not be studied. According to this toxicity scale, the 0th degree of toxicity was detected in 1 (2.4%) patient, the 1st degree - in 25 (60.1%) and the 2nd degree - in 15 (36.6%). Of the local reactions to the therapy, 32 (78.0%) patients had stomatitis, of which 13 (31.7%) patients had grade II-III stomatitis, and the remaining 28 (68.3%) had grade I stomatitis.

Nausea and vomiting were the main criteria for determining general toxicity. Nausea and vomiting of the II degree requiring treatment were noted in 20 (48.8%) patients. Alopecia of the first degree (mild hair loss) was observed in 12 (29.3%) patients.

Before discharge, in the process of dynamic observation, each patient underwent an objective examination and assessment of the status of Karnovsky and ECOG (WHO). At the same time, according to the Karnovsky scale, 90-80% activity and ECOG (WHO) 1 point were

noted in 75.0% of patients. In 17.2% of patients on the Karnovsky scale, 70-60% activity and ECOG (WHO) - 2 points were noted, and in 7.8% of patients, activity on the Karnovsky scale was 50-40% and ECOG (WHO) - 3 points.

After the use of polychemotherapy and radiation therapy, the full effect was achieved in 6 (11.5%) of 52 treated patients and partial - in 31 (59.6%) patients. In 12 (23%) patients, the effect was obtained in the form of tumor stabilization, the progression of tumor growth was noted in 3 (5.7%) patients. Thus, an objective (full + partial) effect on the treatment in this group was observed in 37 (71%) patients.

The total 3-year cumulative survival in group 3 was  $61.3 \pm 4.1\%$ , and the 5-year cumulative survival was  $48.3 \pm 4.9\%$ . About 50% of relapses appeared in the first 2 years after complex treatment. 3-year relapse-free cumulative survival was  $40.9 \pm 4.9\%$ , 5-year -  $31.0 \pm 5.2\%$ .

At the same time, out of 29 patients who received complex therapy, tumor recurrence was noted in 20 (69%) patients. Of these, 2 (6%) patients had a recurrence of regional metastasis.

Of the 23 patients who received chemoradiotherapy without surgery, tumor recurrence was detected in 19 (82.6%) patients, and 25.0% of patients overcame the 5-year period.

Thus, the analysis of the 3- and 5-year total cumulative survival showed that higher rates were noted in the 3rd group of patients who received complex treatment compared with the patients of the 4th group who received combined treatment.

The results obtained once again prove the effectiveness of chemotherapy in the treatment of locally advanced malignant non-epithelial tumors of the maxillofacial region. However, there are also side effects of chemotherapy, in particular the toxicity of chemotherapy drugs. In this regard, we decided to use the technique of neoadjuvant chemotherapy, which will increase the effectiveness of chemotherapy and reduce the side effects of chemotherapy drugs on the body of patients.

For long-term intraarterial chemotherapy (DVAPHT) using the method of catheterization of the external carotid artery or its branches, "Development and introduction into clinical practice of treatment of patients with malignant non-epithelial tumors of the maxillofacial region" with inclusion in the complex of therapeutic measures are described.

The new methodology developed by us is implemented as follows. Having mobilized the external carotid artery and its branches, its ligation is performed above the outlet of the upper thyroid artery. The lingual artery,

departing 1-1.5 cm from the external carotid artery, is taken on clamps, its distal part is bandaged and crossed.

According to the development, after crossing the lingual artery, a catheter is installed in its central part and the end of the catheter is carried retrograde into the external carotid artery, and then into its distal part. The installed catheter is subsequently bandaged together with the lingual artery and the external carotid artery for the

purpose of fixation. The advantage of installing a catheter in the lingual artery is that its diameter is  $2.3 \pm 0.6$  mm and the blood pressure is much less than in the external carotid artery, whose diameter is  $4.4 \pm 0.6$  mm. In this regard, during the removal of the catheter from the lingual artery, bleeding does not occur, which makes it possible to carry out intra-arterial chemotherapy without complications. (fig. 1,2).

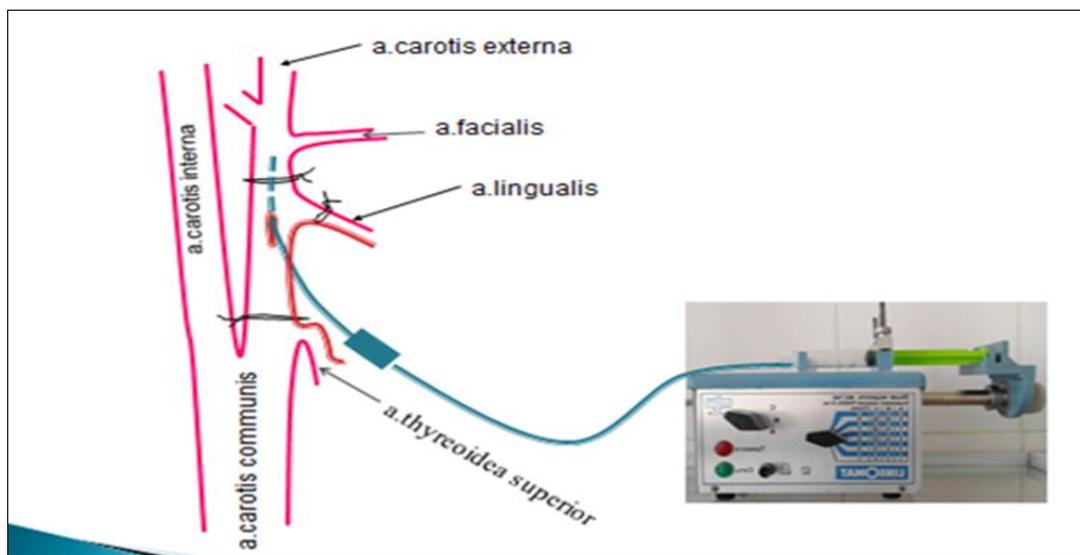


Fig. 1: Method of catheter fixation in the external carotid artery during prolonged intra-arterial chemotherapy in 35 patients.

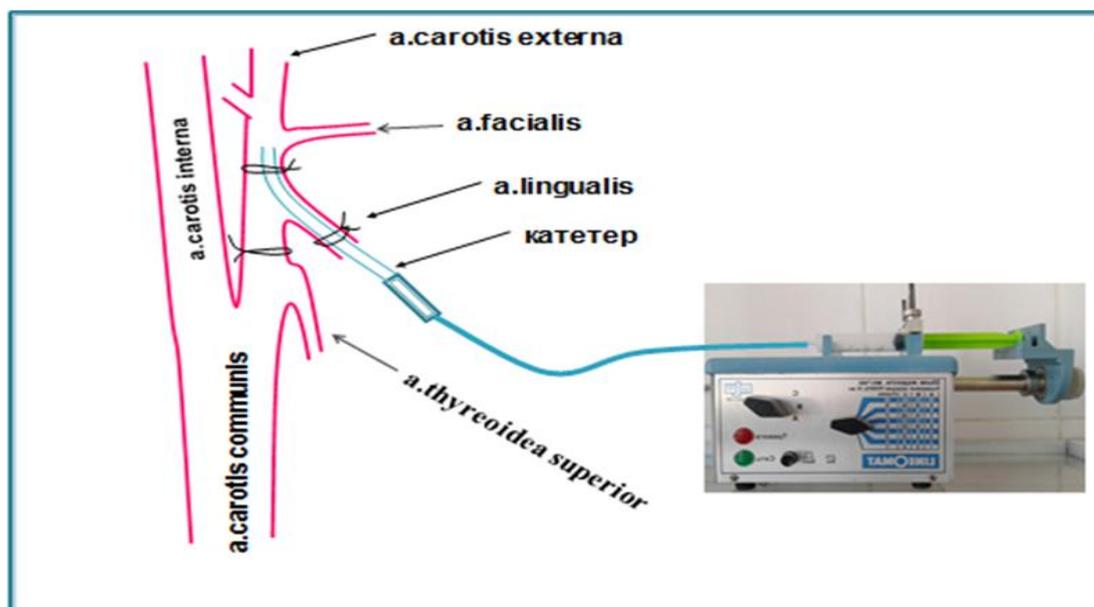


Fig. 2: The scheme of ligation and retrograde catheterization of the lingual artery developed by us.

Inventions No. IAP 05452 2017. "Method of treatment of patients with non-epithelial malignant tumors of the upper jaw", authors: Khasanov A.I., Bekmirzaev R.M.

When comparing catheterization of 2 types, the ratio of pain syndrome, vasculitis and blockage (blood clot) of the catheter are the same in both groups. However, in 12

patients who underwent retrograde catheterization of the lingual artery according to our developed method, there was no bleeding after removal of the catheter from the lingual artery. In 35 patients who underwent catheterization by the traditional method, bleeding of varying degrees was observed after catheter removal in 4

patients. The bleeding was stopped by squeezing with tight tampons and tight bandaging.

To increase the effectiveness of intra-arterial chemotherapy, which was carried out by catheterization of the external carotid artery, in group 1 we used local UHF hyperthermia with a frequency of 40 MHz and radiation therapy, which were performed in 20 patients. At the same time, the local temperature in the tumor focus was increased to 41-43 ° C for 40 minutes. The procedure was repeated 4 times, every other day. A hyperthermia session was performed when patients received cisplatin intraarterially at 15 mg/m<sup>2</sup>. This contributed to the acceleration of blood flow, increased absorption of the drug by tumor cells, as well as the transition of part of the resting cells into the proliferative pool due to the acceleration of metabolic processes.

Group 1 patients underwent a study of the status of Karnovsky and ECOG-WHO at discharge. At the same time, according to the Karnovsky scale, activity of 100% and ECOG 0 points were noted in 10% of patients,

activity of 90/80% and ECOG 1 point – in 80%, activity of 70/60% and ECOG 2 points - in 10%.

Similar data were obtained when using intraarterial polychemotherapy without UHF hyperthermia (group 2 patients). In turn, in the 3rd group, 2 and 3 points were noted in 25% of patients, which is several times more than in the 1st and 2nd groups of patients.

In groups 1 and 2, grade 0 toxicity was detected in 18.5% of patients, whereas in group 3 it was noted only in 2.4% of those treated. The 1st degree of toxicity was noted in 75% of patients with the proposed methods of treatment, and with traditional treatment it is somewhat less. The 2nd degree of toxicity in the 1st group was detected in 5% of patients, in the 2nd - in 7.4%, and in the 3rd - in 36.6% of patients. This indicator is 7 and 5 times more than in patients of the 1st and 2nd groups of patients treated with intra-arterial treatment. Thus, the use of intra-arterial methods of treatment contributed to a decrease in the toxic effect of chemotherapy than with their systemic administration (group 3). (Table 4).

**Table 4: Comparative assessment of the toxic effect of chemoradiotherapy according to the criterion of Toxicity Criterion.**

Groups	Number of patients	Degree of toxicity, degree of				
		0	I	II	III	IV
1	20	20%	75%	5%	-	-
2	27	18,5%	74%	7,4%	-	-
3	41	2,4%	60,4%	36,6%	-	-

Stomatitis was observed in all patients from local reactions to the therapy. At the same time, in groups 1 and 2, 50% and 51.8% of patients, respectively, developed grade II-III stomatitis, and in other cases, grade I stomatitis was observed. In the 3rd group, this indicator was 31.7%, which is 1.6 times less than the indicators of the 1st and 2nd groups. Necrosis of the tissues of the oral mucosa was observed in 1 patient in group 1, neuritis of the facial nerve was also observed in 1 patient in group 2.

A different picture was observed in group 3, where local side complications, tissue necrosis and neuritis of the facial nerve were not observed, which is probably due to less local exposure of chemotherapy drugs to the affected area. Grade II leukopenia was detected in group 1 in 5% of patients, in the 2nd - in 3.7% and in the 3rd - in 12.1%, this is 2-3 times more than in patients who received intra-arterial chemotherapy. As can be seen from Table 3, in the 1st and 2nd groups, the total toxicity was several times less compared to the 3rd group of patients. This phenomenon is characterized by the fact that with intra-arterial administration of chemotherapy drugs, long-term contact of the drug with tumor cells is ensured, in which a concentration of the chemotherapy drug is created in the affected area, 4-6 times higher than the level with intravenous administration. Thus, in

normal organs and tissues, the accumulation of chemotherapy with its intra-arterial administration is 1.5-2 times less than with intravenous administration, due to which the toxic effect of chemotherapy is reduced.

In group 1, as a result of intra-arterial chemotherapy with local UHF hyperthermia and radiation therapy, the immediate full effect was achieved in 7 (35%) of 20 patients, a partial effect was noted in 12 (60%) and tumor stabilization in 1 (5%) patients. Objective (full + partial) effect of treatment in this group was observed in 19 (95%) patients.

The results of treatment of group 2 patients receiving intra-arterial chemotherapy with radiation therapy followed by surgery were approximately similar to the results of group 1 patients. The full effect was observed in 9 (33.3%) of 27 patients, partial – in 14 (51.8%), stabilization - in 3 (11.1%). At the same time, we noted the progression of the disease in 1 (3.7%) patient (Table 5).

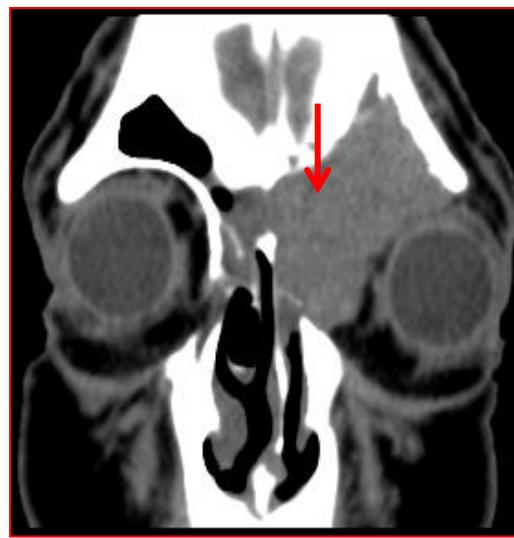
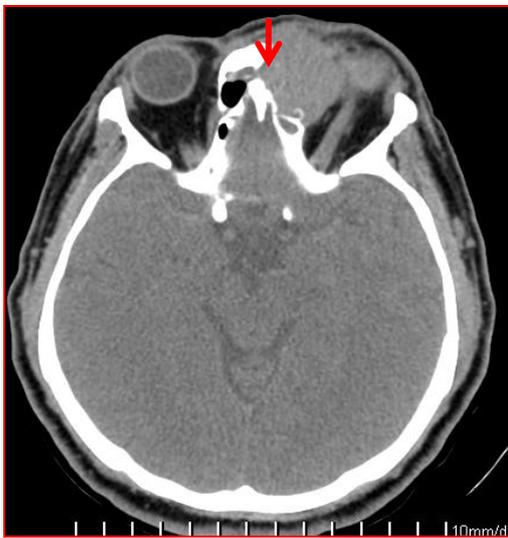
**Table 5: Immediate results of treatment.**

Indicators	Group		
	1, n=20	2, n=27	3, n=52
Immediate effect			
Full	7(35%)	9(33,3%)	6 (11,5%)
Partial	12 (60%)	14 (51,8%)	31(59,6%)
Stabilization	1 (5%)	3(11,1%)	12 (23%)
Progression	-	1 (3,7%)	3 (5,7%)

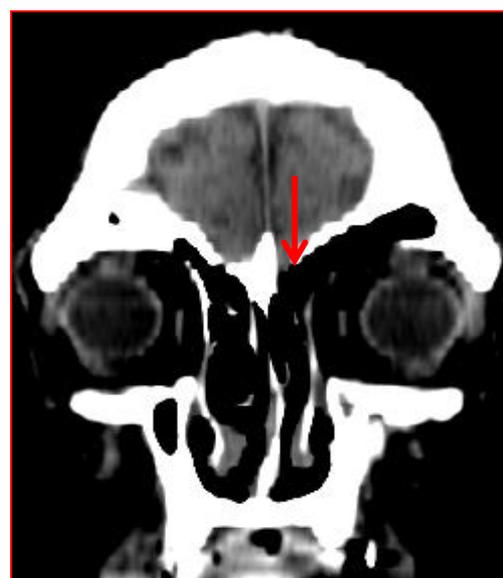
When comparing the results of treatment of the 1st and 2nd groups with the 3rd group, the full effect was observed 3 times more, the results of the partial effect were almost the same, but the stabilization process was noted 4 times higher in the 3rd group of patients. The progression of the disease during treatment was most often noted in group 3. There was no mortality from complications of intra-arterial and systemic

polychemotherapy + radiation therapy. Surgical intervention on the lesion was performed in 72. patients.

As can be seen from the results of the analysis of the immediate effectiveness of treatment, high efficiency was noted in the group of patients who received intra-arterial polychemotherapy, especially in combination with UHF hyperthermia (Figure 3.4).



**Fig. 3: MSCT of patient R. before treatment.**



**Fig. 4: MSCT of patient R. after DVAPCTs and radiation therapy.**

In a comparative study of the number of radical operations performed after neoadjuvant chemotherapy and radiation therapy, higher rates (80%) were noted in the 1st and 2nd groups of patients compared with the 3rd (70%) and 4th (61%) groups. Such a high percentage of radical operations is due to neoadjuvant intra-arterial chemotherapy performed in the 1st and 2nd groups of

patients, which increased the number of patients transitioning from a conditionally unresectable state to a resectable one. At the same time, the opposite trend, i.e. carrying out conditionally radical operations was noted in the 4th and 3rd groups of patients (Fig.5.).

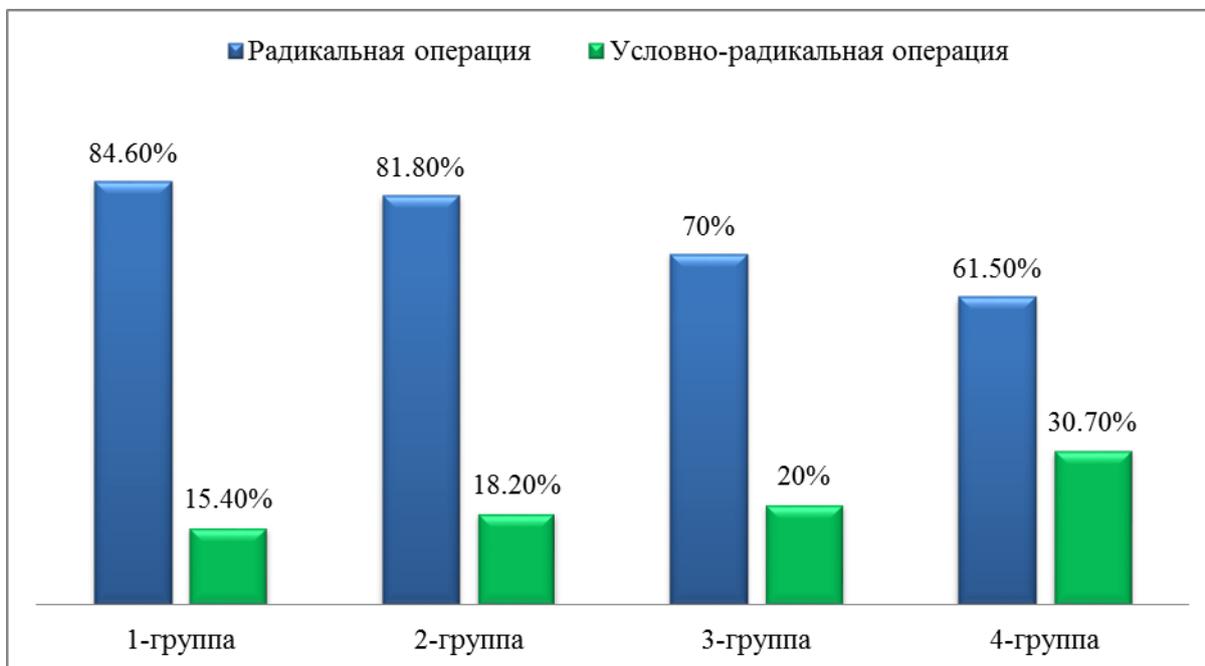


Fig. 5: Comparative evaluation of the characteristics of the performed operations on radicality by groups.

When studying the therapeutic pathomorphosis of the tumor after complex treatment in groups 1, 2 and 3 and combined treatment in group 4 of patients, it was noted that pathomorphosis of the III-IV degree was observed in group 1 in 61.6% of patients, in group 2 - in 63%, in group 3 - in 31% and in group 4 - in 23% of patients. As

can be seen, grade III-IV pathomorphosis was most often found in the 1st and 2nd groups of patients who received long-term intra-arterial chemotherapy. In group 4, grade IV pathomorphosis was not detected. Pathomorphosis of the III degree was most noted in the 3rd and 4th groups of patients (Fig. 6).

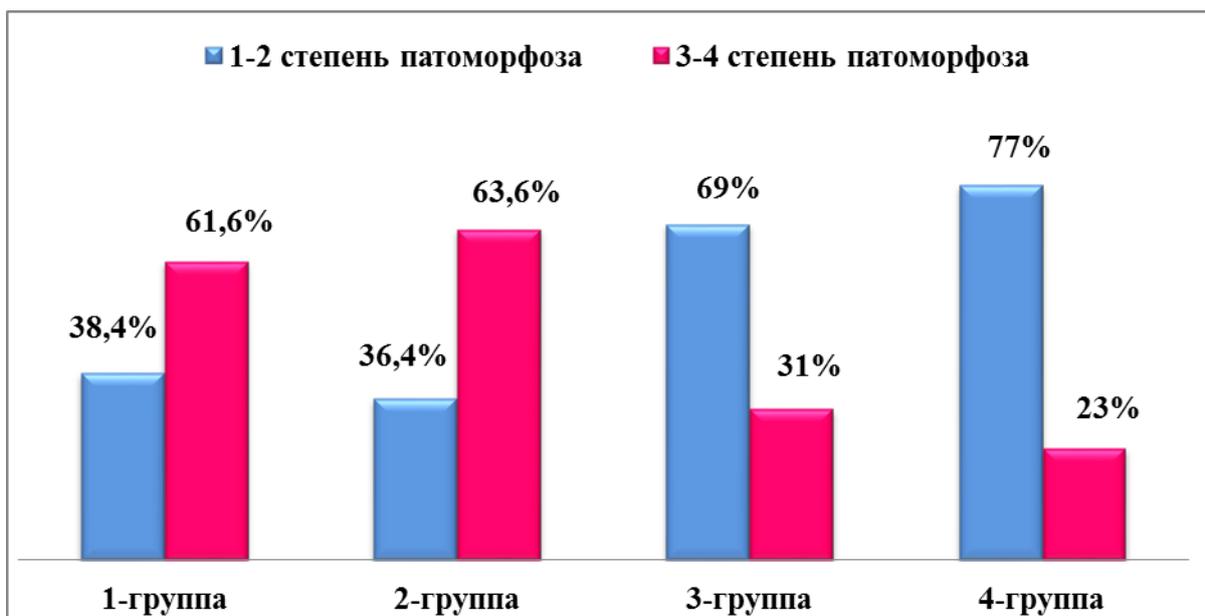


Fig. 6: Study of the therapeutic pathomorphosis of the tumor after treatment by groups.

When comparing the data of patients in the 1st, 2nd, 3rd and 4th groups according to Kaplan E.L. and Meier R., heterogeneous data were obtained (Fig. 7). Thus, in the 1st group of patients, the overall 3-year survival rate was 70.5%, and the 5-year survival rate was 61.5%. In the 2nd group, these indicators were 73.2 and 60.0%, in the 3rd - 61.3 and 48.3%, and in the 4th - 47.1 and 33.3%, respectively ( $p < 0.060$ ). Median survival in groups 1, 2, 3 and 4 was 71, 70, 57 and 44 months, respectively. Survival rates were higher in groups 1 and 2 of patients who received long-term intra-arterial chemotherapy with and without local UHF hyperthermia.

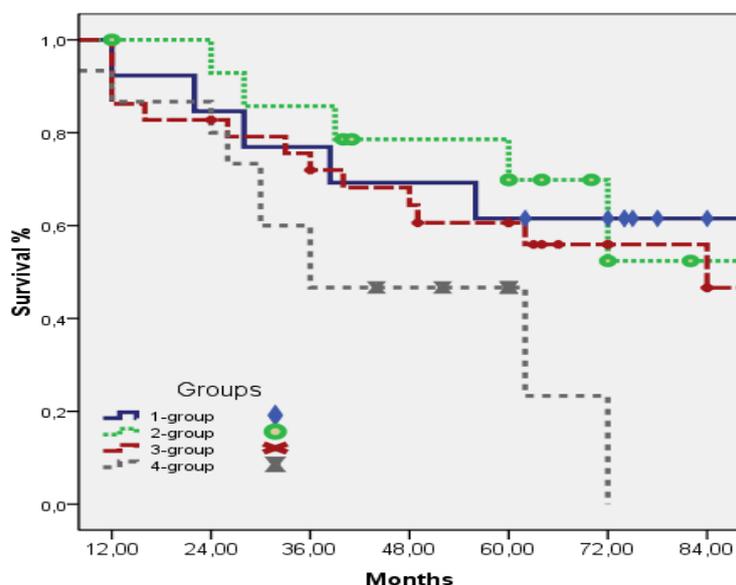
At the same time, cumulative relapse-free survival rates are also high in groups 1 and 2, where patients received DVAPHT with and without local UHF hyperthermia, compared with groups 3 and 4 of patients.

The frequency of relapses in the 1st and 2nd groups compared with the 3rd and 4th groups differed

significantly. If in group 1, tumor recurrence developed in 53.8% of cases, in group 2 - 53.3%, then in groups 3 and 4 - 69.0% and 86.7%, respectively. This once again marks the advantage of long-term intra-arterial chemotherapy. A similar trend is observed in the study of mortality: 38.5% died in group 1, 40.0% in group 2, 51.7% in group 3 and 66.7% in group 4.

When studying the overall survival of patients who did not undergo surgery, the 5-year survival rate in groups 1, 2 and 3 was below 25%. And in the 4th group, who received only radiation therapy, no one lived up to the 5-year term.

Thus, the analysis demonstrated the high efficiency of the proposed method of neoadjuvant long-term intra-arterial chemoradiotherapy.



**Fig. 7: Comparative evaluation of survival curves by Kaplan E.L. and Meier R. by patient groups ( $P < 0.060$ ).**

With tumors of the lower jaw, 5 patients, a titanium plate was installed after surgery, of which 3 (60%) patients underwent segmental resection of the lower jaw body, 1 (20%) patients underwent resection of the anterior fragment of the lower jaw, and the remaining 1 (20%) underwent resection of the angle of the lower jaw. In this group, patients underwent reconstructive reconstructive operations in various variants in order to restore the continuity of the mandibular arch to prevent possible functional and cosmetic disorders. At the same time, the functional state of the mandible and the quality of life of patients were significantly reduced during resection of the anterior fragment of the mandible, which are associated with tension and load in the anterior zone. And with lateral segmental resection of the lower jaw body, functional disorders and deterioration in the quality of life of patients are completely eliminated.

When studying postoperative complications, 1 patient developed an orostoma 10-15 days after surgery. This is due to the fact that they received DTHT 40-gray before the operation.

## DISCUSSION

Non-epithelial tumors of the maxillofacial region belong to a group of tumors that are characterized mainly by the local-regional nature of the spread. In these tumors, good treatment results can be achieved using a combination of local treatment methods - radiation therapy and surgery.<sup>[20]</sup> In locally advanced forms of the disease, the use of neoadjuvant chemotherapy leads to tumor regression in 20-50% of patients,<sup>[21]</sup> which indicates the expediency of adding chemotherapy to local treatment methods.

According to Rogelio Gonzalez et al. (2011), more than 50 histological subtypes of soft tissue sarcoma and a diverse clinical course of the latter have been identified.<sup>[6,22,23,24,25]</sup> They can vary with the flow, having a relatively slow growth, causing a small destructive growth, and be locally aggressive, regionally destructive and have a great potential for metastasis. They have a diverse histological structure, but the most common are malignant fibrous histiocytoma and fibrosarcoma.<sup>[6,25]</sup>

In the scientific works of Nishino H. et al. (2003),<sup>[2]</sup> and Hye Sung Won et al. (2009).<sup>[26]</sup> it is shown that the complexity of anatomy and the proximity of the orbit, brain, and cranial nerves complicate the conduct of radical operations. This leads to visual impairment and cosmetic defects, forcing patients to avoid surgical treatment.<sup>[27,28,29,30]</sup>

Methods of regional intra-arterial chemotherapy of locally advanced malignant tumors of the maxillofacial region are widely used in the world. The use of regional intra-arterial chemotherapy by injecting the drug into an arterial vessel that supplies blood to the tumor location zone allows for maximum damage to the tumor with minimal exposure to chemotherapy drugs on various organs and body systems.<sup>[9,10,11,12,31,32]</sup>

Based on experimental and clinical data, the authors believe that the duration of intra-arterial administration of an antitumor drug should be 6-12 days.<sup>[33]</sup> Increasing the concentration of cytostatics is one of the most effective methods for suppressing primary drug resistance.<sup>[12]</sup> Intra-arterial administration of antitumor drugs can increase its concentration in regional tissues by 3-5 times compared to that with intravenous administration of the same doses.<sup>[10,33,34]</sup>

Literature data on the use of intra-arterial chemotherapy in the treatment of malignant tumors of the maxillofacial region show a fairly high efficiency of the immediate results of treatment. So, Kornietskaya A.L. et al. (2007) in 17 patients with sarcoma, polychemotherapy was performed according to the doxorubicin 45 mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup> intraarterially for 1-2 days,<sup>[35]</sup> cyclophosphane 800 mg/m<sup>2</sup> was administered intravenously on day 3. The interval between courses was 14 days. A partial effect or stabilization of the tumor process was observed in 13 (76.4%) patients. Therapeutic pathomorphosis of the 3rd degree was noted in 3 cases, pathomorphosis of the 2nd degree - in the 7th and 1st degree (or its absence) – in 7 cases, respectively.

Hye Sung Won et al. (2009), analyzing the results of treatment of patients receiving intra-arterial chemotherapy, intravenous chemotherapy and chemoradiotherapy, showed that the immediate objective (full + partial) effect was noted in 70, 53 and 57%, toxicity (nausea and vomiting) were noted in 70, 87 and 86%, according to the methods of administration of drugs.<sup>[26]</sup> At the same time, the authors performed intra-

arterial chemotherapy by means of Seldinger catheterization, when a catheter is inserted through the femoral artery into the external carotid artery using angiography.

The mechanism of action of hyperthermia on biological tissues is multifaceted and manifests itself at the molecular, cellular and tissue levels. Hyperthermia has its own damaging effect at the cellular level, and this effect depends on the value of temperature and the duration of heating, hence the requirement for localization of hyperthermic effects in the tumor area.<sup>[36]</sup> With hyperthermic exposure, in contrast to the action of ionizing radiation, a decrease in the concentration of oxygen in the tissues does not lead to a weakening of the damaging effect. Thus, hyperthermia makes it possible to overcome the radioresistance of hypoxic tumor cells.<sup>[37,38,39]</sup>

Biologically inert structures made of titanium are most widely used for the reconstruction of a postoperative defect in tumors of the lower jaw. Reconstructive titanium plates are used to eliminate segmental defects of the lower jaw.

According to Dedikov D.D. 2020. Currently, the technique of reconstruction of mandibular defects using titanium reconstructive plates and titanium screws is widely used. This technique is used in general practice as a reliable method of fixation. The use of structurally different dynamic reconstructive titanium plates to compensate for the defect of the lower jaw, on the one hand, is an affordable and simple way, and on the other hand, when applied according to clear indications, it allows achieving acceptable functional and aesthetic indicators. These plates are easily adapted intraoperatively by the surgeon according to the extent and shape of the defect.<sup>[40,41,42]</sup>

## CONCLUSION

Thus, the analysis showed that in the 1st and 2nd group of patients, the study of the immediate and long-term results of the proposed method of treatment showed high efficiency of neoadjuvant long-term intra-arterial chemoradiotherapy. In groups 1 and 2, the immediate and long-term results of treatment are much better than in group 3, when patients received chemoradiotherapy, and the drug was administered intravenously by drip, also compared with group 4 patients who received combined (radiation therapy + surgery) treatment. These results are due to the fact that during intra-arterial chemotherapy, the maximum volume of chemotherapy drugs accumulates in the tumor, several times more than in other organs and systems of the body, which led to a decrease in the toxic effects of chemotherapy drugs on the body as a whole.

The use of the method of retrograde catheterization of the lingual artery developed by us for the first time

eliminates bleeding after removal of the catheter from the lingual artery.

With the use of titanium plates in reconstructive and reconstructive operations in patients with tumors of the mandible in the postoperative period, the quality of life of patients and the functional state of the mandible improves.

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