ORIGINAL ARTICLE

CONTENTS

Effectiveness of treatment of oropharyngeal carcinoma patients

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ABSTRACT

Aim: To analyze the results of treatment of patients with oropharyngeal carcinoma.

Materials and Methods: 276 patients with oropharyngeal carcinoma were treated in 2008-2021. Neoadjuvant chemotherapy consisted of three to six cycles: paclitaxel 175 mg/m^2 and carboplatin 350 mg/m^2 (or cisplatin 100 mg/m^2) on the first day. The interval between cycles was 21 days. After the cycles, all patients were prescribed a course of radiation therapy in a total focal dose (TFD) of 65 Gy. The outcome of treatment was assessed by the degree of tumor regression according to RECIST criteria one month after the end of combination treatment. Statistical processing was performed using STATISTICA 6.1 software (StatSoftInc).

Results: The three- and five-year survival rates of the examined patients with oropharyngeal carcinoma after treatment were 40.8% respectively (95% CI 33.7 - 47.9) and 27.0%, (95% CI 20.6 - 33, 4) with a median survival of 36 months with 95% CI (35.5 - 40.2). Processing was performed using STATISTICA 6.1 software (StatSoftInc).

Conclusions: Analysis of treatment of patients with oropharyngeal carcinoma with predominance of squamous cell carcinoma (90.6%), localized primarily in the palatine tonsil (73.2%), with the most common stages $T_3N_1M_0$ (30.1%) and $T_3N_1M_0$ %), with regional metastases to the lymph nodes of the neck (89.9%), showed that the effectiveness of treatment of patients is quite high, because in most of the examined in the short term after combined treatment there was complete or partial regression of the tumor (91.7%),
no progression of the oncological process was detected in any of them.

KEY WORDS: oropharyngeal carcinoma, survival rate, treatment of patients with oropharyngeal carcinoma, chemotherapy

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INTRODUCTION

According to the National Cancer Registry, the incidence of oropharyngeal carcinoma in Ukraine is 6.5 per 100 thousand population. At the time of diagnosis, more than 75.0% of patients have stage III-IV, and mortality up to one year is 40.1% [1]. In recent decades, approaches to combination therapy of patients with squamous cell carcinoma in most sites of the head and neck have changed significantly. Non-surgical organ-preserving approaches with the use of neoadjuvant chemotherapy and subsequent radiation therapy have demonstrated effectiveness and are widely used in the treatment of patients with squamous cell carcinoma of the oral pharynx [2].

The task of this work was to conduct neoadjuvant chemotherapy for patients with oropharyngeal cancer at the first stage and to determine its effectiveness in different localizations of the tumor in the pharynx and depending on the association with the papilloma virus.

We present the results of such treatment in our study.

AIM

Aim of the work is to analyze effectiveness of treatment of patients with malignant neoplasms of the oral pharynx to improve scientifically substantiated medical technology of treatment.

MATERIALS AND METHODS

The prospective study included 276 treatment-naïve patients with malignant neoplasms of the oral pharynx, who were treated in the Department of Oncopathology of the ENT organs of the State Institution «Institute of Otolaryngology named after prof. O.S. Kolomiychenko of National Academy of Medical Sciences of Ukraine « in 2008-2021. The study included 219 (79.3%) men and 57 (20.7%) women. The age of patients ranged from 26 to 83 years, the mean age was 55.65 years with a 95% confidence interval (CI) 54.46 - 56.84 years. In all cases, the diagnosis was verified histologically. The localization, stage, TNM classification and other characteristics of the tumor were evaluated.

Treatment started with three to six cycles of neoaduvant chemotherapy: paclitaxel 175 mg/m^2 on the first day and carboplatin 350 mg/m^2 (or cisplatin 100 mg/m^2) on the second day. Three weeks later, chemotherapy was repeated. With tumor regression by 50%, up to six courses of chemotherapy were carried out.After three or six cycles of chemotherapy, radiation therapy in a total focal dose (TFD) of 65 Gy was prescribed. It was performed in all patients regardless of tumor regression after chemotherapy. The outcome of treatment was assessed by the degree of tumor regression according to the RECIST criteria one month after combination treatment on the basis of contrast-enhanced CT studies, therapeutic pathomorphosis data and clinical examination of the patient. Subsequently, appropriate treatment was prescribed for residual tumor and existing regional metastases or progression. Statistical processing was performed using STATISTICA 6.1 software (StatSoftInc. ROC analysis was performed in the software package MedCalc Statistical Software trial version 20.015 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2021). Relative values were calculated with a 95% confidence interval (95% CI) by the Wald normal approximation method. The comparison of relative values was performed according to the Pearson Chi-square ($\chi 2$) criterion (including the Yates correction for continuity for low frequencies) [3-5]. To assess the relationships of ordinal and numerical variables, a rank correlation analysis was performed with the calculation of Spearman correlation coefficients (r_s), the association was evaluated by the criterion phi-square (φ). ROC-analysis (Receiver Operating Characteristic) was performed with the calculation of standard operating characteristics: sensitivity, specificity and area under the ROC-curve (area under ROC curve - AUC) with 95% CI [6, 7]. The analysis of patient survival was performed by constructing mortality tables and the Kaplan-Meier method. Differences in the survival of different groups were determined by the log-rank criterion (log-rank test - logarithmic rank test). Comparison of survival rates in more than 2 groups was performed according to Chi-square statistics on the basis of a generalized logarithmically ranked test [8-10] . To analyze the influence of the studied factors on survival rate, we used a regression model of proportional risks (Cox proportional-hazards regression) with the calculation of the hazard ratio (HR hazard ratio) [9,11-13] . The critical value of the level of statistical significance (p) for all types of analysis was taken as <5% ($p < 0.05$).

The study included measures to ensure the safety and health of patients, respect for their rights, human dignity and moral and ethical standards in accordance with the principles of the Helsinki Convention on Human Rights, set out in the document «Bioethics of the Helsinki Declaration on the Moral Regulation of Medical Research». Council of Europe Convention on Human Rights and Biomedicine and relevant laws of Ukraine.

RESULTS

Microscopic examination of tumors showed a significant predominance of squamous cell carcinoma. Thus, 250 (90.6%) patients were histologically diagnosed with squamous cell carcinoma (SCC): keratinized in 118 (42.8%) patients and non-keratinized in 132 (47.8%) patients; in 17 (6.2%) patients - low-grade cancer and in 5 patients (1.8%) - transitional cell carcinoma, in the rest (4 patients - 1.4%) - other forms. (Fig. 1). Most often the tumors were localized in the palatine tonsil - 202 (73.2%) patients, on the lateral and posterior walls of the oropharynx - in 38 (13.8%) patients, on the vallecular sinus and on the lingual surface of the epiglottis - in 28 (10.1%) patients, on the soft palate – in 8 (2.9%) patients. (Fig. 2). According to the classification of the ICD of the 10th revision, the diagnoses of patients according to localization were represented by the codes C05.1-soft palate, C09.9-palatine tonsil, C10.0-vallecular sinus and C10.2-lateral wall of the oropharynx. Stage II was in 16 patients (5.8%), stage III - in 139 patients (50.4%) and stage IV - in 121 patients (43.8%). In 248 patients (89.9%) regional metastases to the lymph nodes of the neck were found, of which 71 (28.6%) patients had bilateral metastases. The most commonly lesions of IIA, IIB and III levels of lymph nodes of the neck according to the classification of K. Robbins were diagnosed.

The distribution of the examined patients with malignant neoplasms of the oral pharynx by stage of the disease and TNM classification is presented in (Table 1).

By the estimates, according to the International TNM classification, patients with a prevalence of T3 tumor prevailed - 180 patients (65.2%), stage T2 was determined in 77 patients (27.9%), stage T4 - in 19 (6.9%)); N0 was determined in 30 patients (10.9%), N1 - in 126 (45.65%), N2 - in 119 (43.1%) and N3 - in one patient (0.35) %). All subjects had no signs of distant metastases (M0). The most common characteristics of the tumor process (Fig. 3) were $T_3N_1M_0$ - 83 (30.1%) and $T_3N_2M_0$ - 66 (23.9%), which were observed mainly in patients with stage III of the disease. $T_2N_0M_0$ was revealed with insignificant frequency - in 9 patients (3.3%), $T_4N_2M_0$ - 5 (1.8%), $T_3N_3M_0$ - 1 (0.4%), $T_4N_0M_0$ - 1 (0.4%).

After completion of chemotherapy and radiation therapy in patients with malignant neoplasms of the oral pharynx, none of the subjects showed tumor

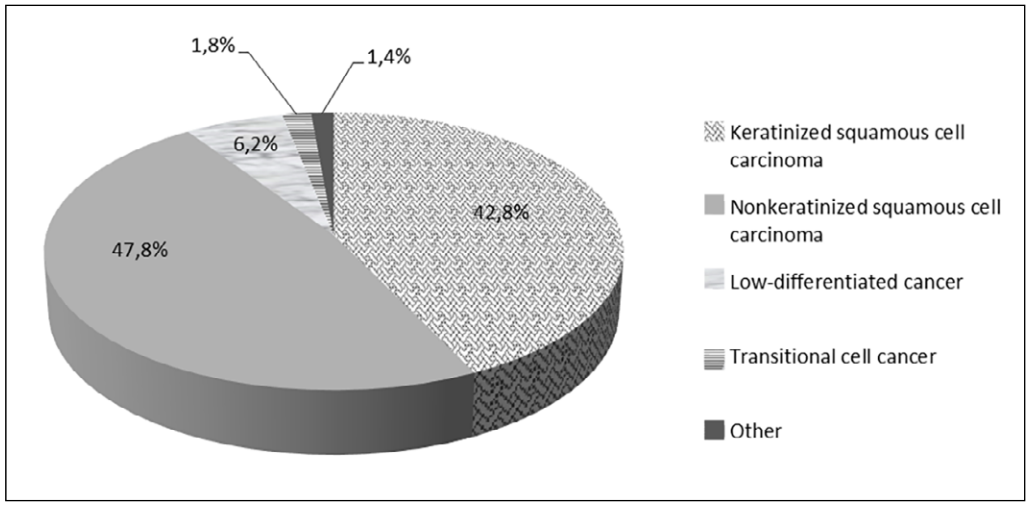

Fig. 1. Distribution of the examined patients by morphological characteristic of the tumor (in % per 100 of the examined).

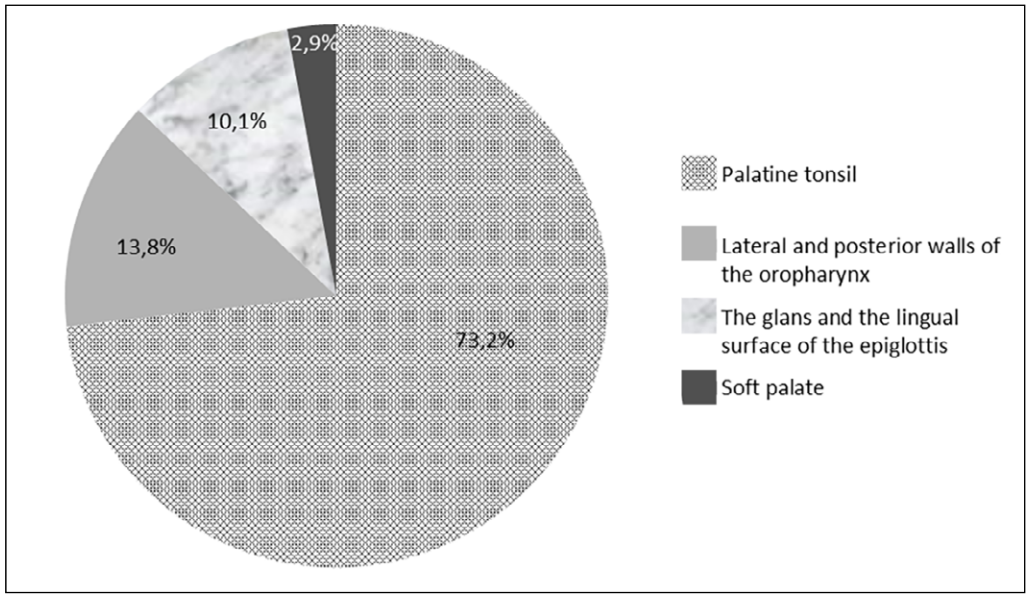

Fig. 2. Distribution of the examined patients by localization of the tumor (in % per 100 of the examined).

progression, 102 (37%) showed complete tumor regression, 151 (54.7%) - partial regression and 23 (8.3%) - stabilization of the disease(Table 2).

The largest proportion of patients with complete tumor regression was determined in patients with stage II - 12 (75.0%), which was statistically significantly higher (*p <0.001*) compared to patients with stage III and IV (46.0% and 21.5% respectively). Between the results of combination therapy and the stage of the disease, a significant rank correlation was determined (Spearman's correlation coefficient $r_s = 0.29$; *p <0.001*), and it was also influenced by the correlation analysis, morphological characteristics of the tumor ($r_s = 0.14$; *p = 0.024*), keratinization of the tumor ($r_s = 0.16$; $p = 0.006$), T stage ($r_s = 0.41$; *p <0.001*) and N stage ($r_s = 0.241$; *p <0.001*).

Of the total number of subjects, 18 patients (6.5%) underwent appropriate surgery. Of those operated on, 4 (22.22%) patients underwent laryngectomy, 13 (72.22%) - cervical dissection, and 1 patient underwent both surgeries.

Almost a quarter of patients - 64 (23.2%) underwent immunohistochemical (IHC) study of $p16^{INK4}$ gene expression. When evaluating the immunohistochemical analysis with the tumor suppressor $p16^{INK4}$, a negative reaction was found in 27 (42.2%) patients, while in 37 patients (57.8%) the presence of a mixed (nuclear-cytoplasmic) reaction of individual cells with the marker was determined. A significant associative and rank correlation ($r_s = 0.33$; *p = 0.007*) was determined between the reaction with the biomarker $p16^{INK4}$ and the direct results of the combined treatment, which is due to the presence of tumor suppressor $p16^{INK4}$ in patients with complete and partial regression of the tumor and its absence in patients. with stabilization. In compete regression the proportion of patients with the present reaction with the tumor suppressor $p16^{INK4}$ makes up 75,9% whereas in partial - 42,9% (*p = 0.029*) (Table 3).

The chances of achieving complete tumor regression increase by 4.2 times in the presence of a reaction with the tumor suppressor $p16^{INK4}$ compared to its absence

Table 1. Distribution of the examined patients by disease stages and classification (absolute number and %)

Stagen (%)	T - tumor n (% of patients of a certain stage)			N – regional lymph nodes n (% of patients of a certain stage)				TNM	Number of patients	
	T_2	T_3	T_4	N_0	N_1	N_2	N_3		abs.	%
II 16 (5,8)	14 (87,5)	2 (12,5)	0 (0)	9 (56,25)	4 (25,0)	4 (18,75)	0 (0)	$T_2N_0M_0$	9	3,3
								$T_2N_1M_0$	4	1,4
								$T_2N_2M_0$	1	0,4
								$T_3N_2M_0$	2	0,7
III 139 (50,4)	29 (20,9)	110 (79,1)	0 (0)	20 (14,4)	108 (77,7)	11 (7,9)	0 (0)	$T_2N_1M_0$	26	9,4
								$T_2N_2M_0$	3	1,1
								$T_3N_0M_0$	20	7,2
								$T_3N_1M_0$	83	30,1
								$T_3N_2M_0$	8	2,9
IV 121 (43,8)	34 (28,1)	68 (56,2)	19 (15,7)	1 (0,8)	14 (11,6)	105 (86,8)	1 (0,8)	$T_2N_2M_0$	34	12,3
								$T_3N_1M_0$	1	0,4
								$T_3N_2M_0$	66	23,9
								$T_3N_3M_0$	1	0,4
								$T_4N_0M_0$	1	0,4
								$T_4N_2M_0$	5	1,8
								$T_4N_1M_0$	13	4,7
In total	77 (27,9)	180 (65,2)	19 (6,9)	30 (10,9)	126 (45,65)	119 (43,1)	1 (0,35)		276	100

Table 2. Short-term results of combination treatment of patients with oropharyngeal carcinoma by diseases stages (absolute number and %)

Result	II stage n=16		III stage n=139		IV stage n=121		In total n=276	
	abs.	%	abs.	%	abs.	%	abs.	%
Full regression	12	75,0	64	46,0	26	21,5	102	37,0
Partial regression	4	25,0	64	46,0	83	68,6	151	54,7
Stabilization	0	0	11	8,0	12	9,9	23	8,3
Differences between groups	χ^2=27,69 (p<0,001)							

(the odds ratio (OR) = 4.2; 95% CI (1.3 - 12.3); *p = 0.010*). Regarding the informativeness of the biomarker for predicting tumor regression, according to ROC-analysis, which shows the dependence of the number of correctly classified results (true positive) on the number of incorrectly classified results (false negative), no convincing evidence of discriminant ability of $p16^{INK4}$ was obtained, it is defined as medium. Operational characteristics according to ROC analysis: sensitivity - Se = 75.86%; specificity Sp = 57.14%, area under the ROC curve - AUC = 0.665 and 95% CI (0.536 - 0.778); *p = 0.005* (Fig. 4).

The area under the ROC curve for the prognostic ability of complete tumor regression reached a statistically significant level (*p = 0.005*), but is not of sufficient clinical significance, because AUC <0.700, being the prognostic characteristic of $p16^{INK4}$ is considered average.

It should be noted that in $p16^{INK4}$ at a low level of specificity - Sp = 57.14%, a fairly high level of sensitivity - Se = 75.86% was noted, which indicates a high proportion of true positive results and a small number of false positive results. This is more appropriate for the initial conclusion on tumor regression.

Indicators of disease-specific (disease-dependent) cumulative survival rate for all examined patients with oropharyngeal cancer over the study period by the median value were 36 months with 95% CI (35.5 - 40.2). The probability of living a year or more was 97.3% (95% CI 94.9 - 99.7); three and more years - 40.8% (95% CI 33.7 - 47.9); five and more years - 27.0% (95% CI 20.6 - 33.4) (Table 4, Fig. 5).

According to the analysis of survival rate, there were no differences in the that of in patients divided into age groups (up to and over 65 years), morphological characteristics of the tumor, reactions with the tumor suppressor $p16^{INK4}$ (*p> 0.05*). The higher level of median survival in women compared to men was determined - 34.0 months (95% CI 30.0 - 60.0) compared to 30.0

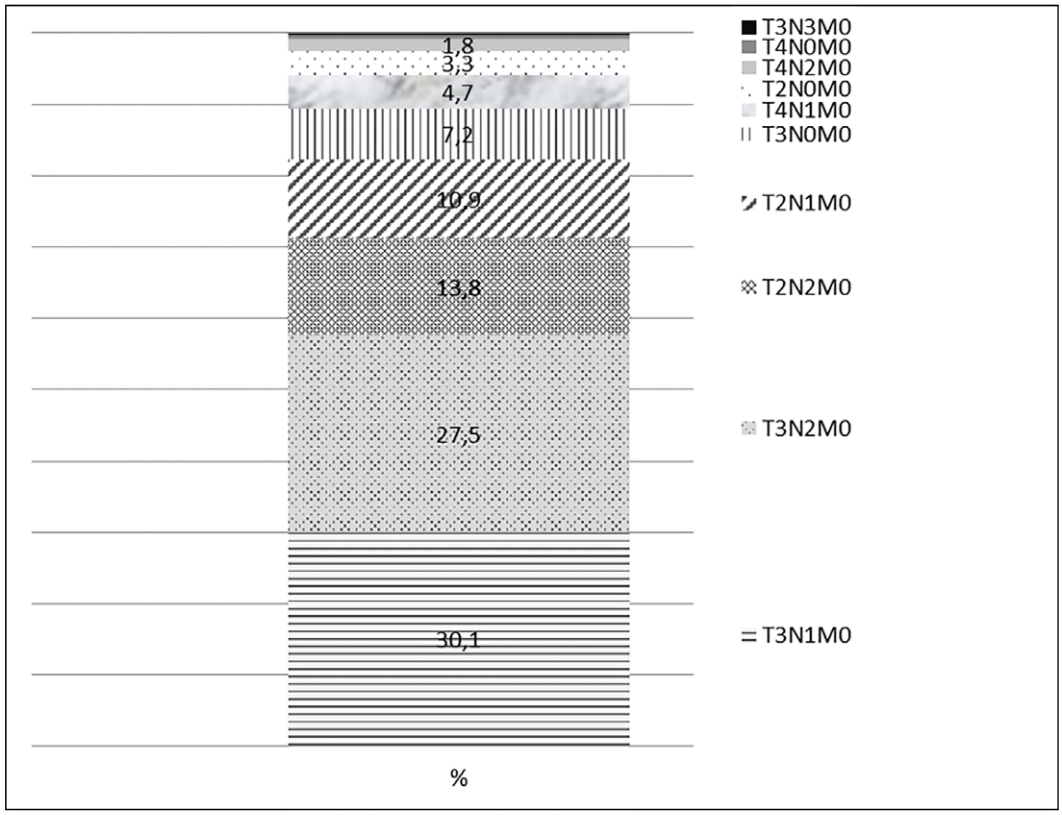

Fig. 3. Distribution of the examined patients by TNM stage (in % per 100 of the examined).

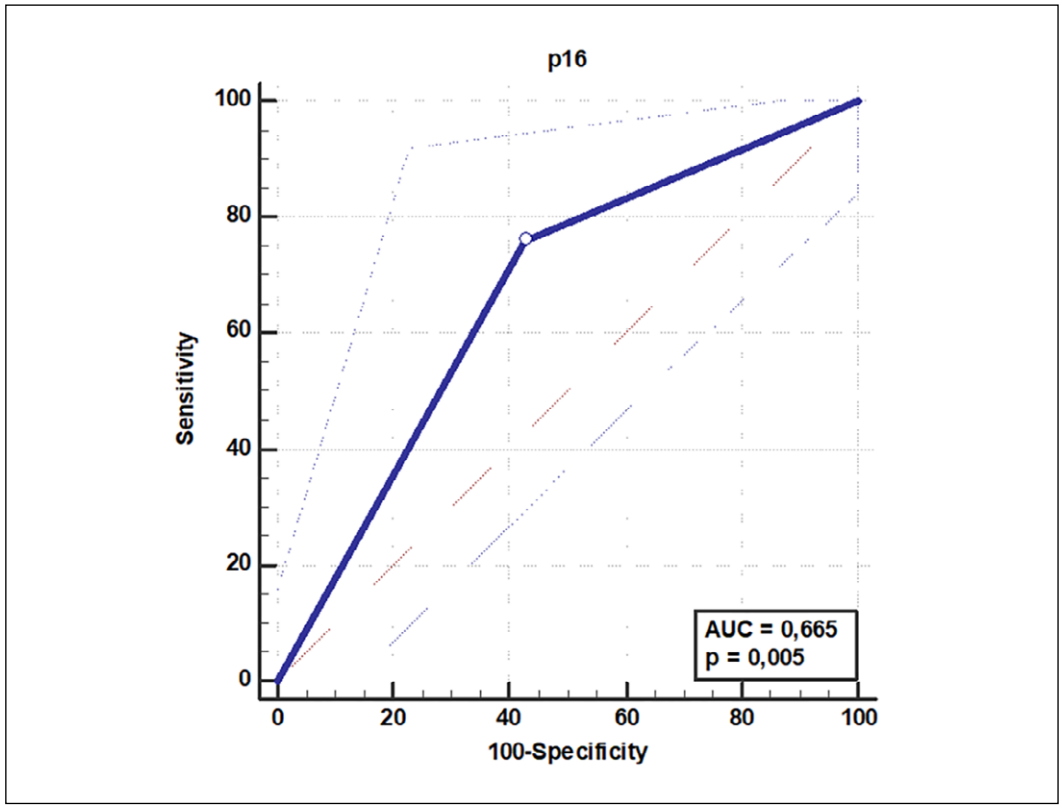

Fig. 4. ROC curve for evaluating prognostic capabilities of complete regression of the tumor by p16INK4 expression in the examined patients.

months (95% CI 20.0 - 36.0)); the one-, three-, and five-year survival rates of the women surveyed were also higher. Differences in survival rate of patients by gender were characterized by the presence of statistically significant differences ($p = 0.013$) (Fig. 6).

When comparing survival rates in different age groups, no statistically significant differences were found ($p = 0.109$), but there is a tendency to decrease with age: in patients under 65 years, three-year and five-year survival rates are 45.5%, respectively (95%

Table 3. Indicators of reaction with tumor suppressor $p16^{INK4}$ in the examined patients depending on results of combination treatment

Result	Reaction with an oncosupressor $p16^{INK4}$, n (%)		Discrepancies and associations *
	Negative	Available	
Full regression (n=29)	7 (24,1)	22 (75,9)	p=0,029* φ=0,33 r_s=0,33 (p=0,007)
Partial regression (n=35)	20 (57,1)	15 (42,9)	
Stabilization (n=0)	0 (0)	0 (0)	
All were examined for tumor markers (n=64)	27 (42,2)	37 (57,8)	-

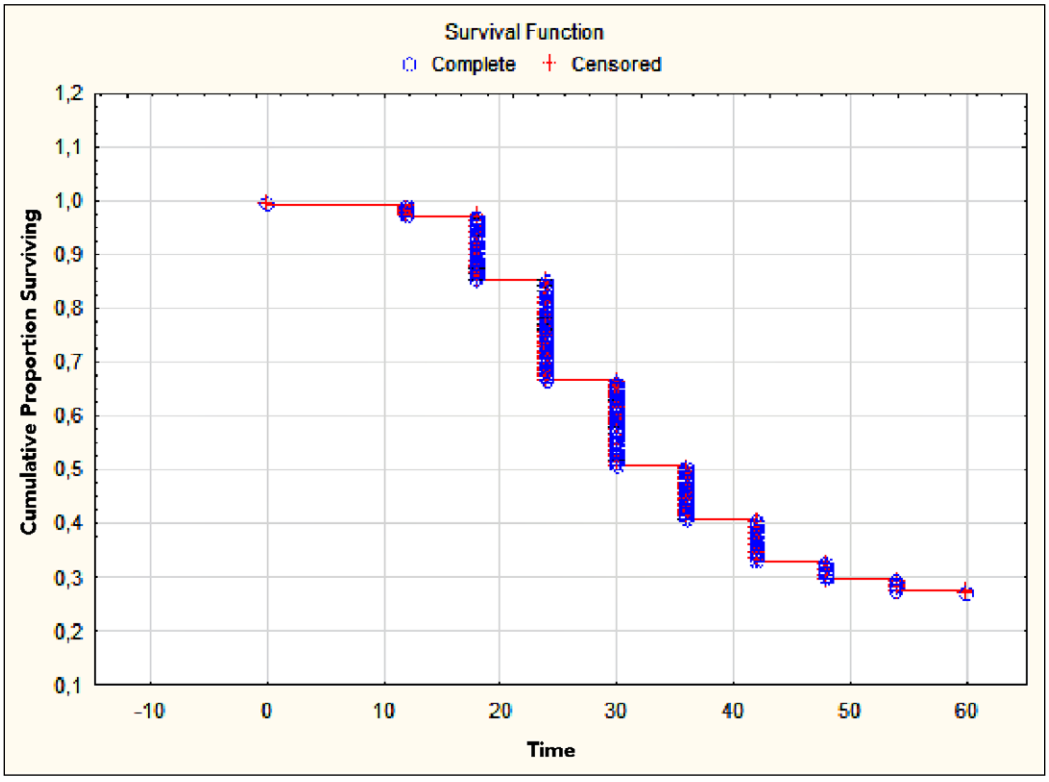

Fig. 5. Cumulative survival rate of the examined patients with oropharyngeal carcinoma (survival period in months).

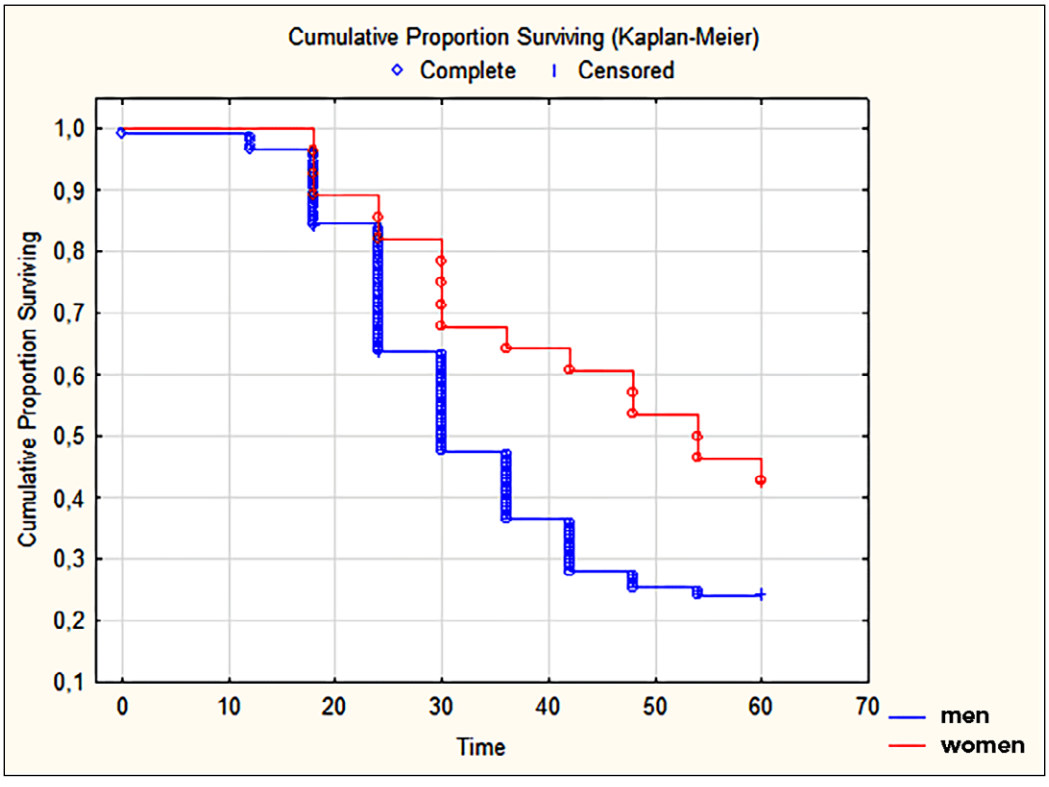

Fig. 6. Cumulative survival rate of the examined patients with oropharyngeal carcinoma depending on gender (survival period in months).

Table 4. Indicators of two-year, three- and five-year survival rate in the examined patients with malignant oropharyngeal neoplasms after treatment

Survival by individual groups	Overall cumulative survival (%)						Median survival		
	1-year-old		3-year-old		5-year-old		Mon-ths	25 %; 75 %	95 % CI
	%	95 % CI	%	95 % CI	%	95 % CI			
Overall survival	97,3	94,9 - 99,7	40,8	33,7 - 47,9	27,0	20,6 - 33,4	36,0	24,0; n/d	35,5 - 40,2
Gender									
men	96,8	94 - 99,6	36,5	28,9 - 44,1	30,9	17,3 – 32,9	30,0	24,0; 52,2	30,0 - 36,0
women	100,0	77,8 – 100,0	64,3	46,5 - 82,1	42,9	24,6 - 61,2	54,0	30,0; n/d	30,0 - 60,0
p *the level of disagreement by the log-rank test*									*0,013*
Age									
up to 65 years old	96,7	93,5 - 99,9	45,5	36,6 - 54,4	31,2	22,9 - 39,5	36,0	24,0; n/d	30,0 - 42,0
65 years of age and older	89,1	81,5 - 96,7	31,8	20,3 - 43,3	9,1	-0,6 - 18,8	30,0	24,0; 42,0	24,0 - 36,0
p *the level of disagreement by the log-rank test*									*0,109*
Morphological characteristics of the tumor									
keratinized squamous cell cancer	98,8	96,4 - 99,2	32,3	22,1 - 42,5	22,4	13,3 - 31,5	30,0	24,0; 47,3	30,0 - 36,0
non-keratinized squamous cell carcinoma	96,2	92 - 98,4	45,6	34,6 - 56,6	30,4	20,3 - 40,5	36,0	24,0; n/d	30,0 - 42,0
others	95,7	87,4 – 100,0	55,2	34,4 - 76	32,2	12,6 - 51,8	42,0	24,0; n/d	24,0 - 54,0
p the level of differences according to χ2 based on the generalized log-rank test									*0,336*
Diagnosis according to the international classification of diseases									
C05.1	n/d	n/d	n/d	n/d	n/d	n/d	24,0	18,0; 37,5	18,0 - 42,0
C09.9	98,4	96,2 - 100,0	51,4	42,6 - 60,2	33,5	25,2 - 41,8	42,0	24,5; n/d	36,0 - 48,0
C10.0	96,0	88,3 - 99,7	24,0	7,3 - 40,7	n/d	n/d	30,0	18,0; 36,0	24,0 - 36,0
C10.2	93,1	83,9 - 99,3	10,3	-0,8 - 21,4	n/d	n/d	24,0	24,0; 30,0	24,0 - 30,0
p the level of differences according to χ2 based on the generalized log-rank test									*<0,001*
Stage of the disease									
II	87,5	64,6 - 95,4	62,5	29,0 – 96,0	n/d	n/d	42,0	30,0; n/d	0,0 - 42,0
III	98,9	96,8 – 100,0	55,7	45,4 - 66	39	28,9 - 49,1	42,0	30,0; n/d	36,0 - 60,0
IV	96,5	92,6 - 100,0	22,7	13,7 - 31,7	11,9	5,0 - 18,8	24,9	24,0; 36,0	n/d
p the level of differences according to χ2 based on the generalized log-rank test									*<0,001*
The stage of the tumor process according to the TNM classification (tumor – T)									
T_2	96,8	90,6 – 100,0	58,1	40,7 - 75,5	41,9	24,5 - 59,3	48,0	28,5; n/d	30,0 - 60,0
T_3	98,5	96,4 - 99,6	42,6	34,2 - 51	27,4	19,8 - 35	36,0	24,0; n/d	30,0 - 42,0
T_4	89,5	75,7 - 96,3	n/d	n/d	n/d	n/d	24,0	18,0; 24,0	18,0 - 30,0
p the level of differences according to χ2 based on the generalized log-rank test									*<0,001*
Tumor stage according to TNM (regional lymph nodes – N)									
N_0	95,2	86,1 – 98,0	60,5	39,1 - 81,9	n/d	n/d	48,0	30,0; n/d	30,0 - 48,0
N_1	96,3	92,2 - 99,4	50,6	39,7 - 61,5	37	26,5 - 47,5	42,0	24,0; n/d	30,0 - 48,0
N_{2-3}	98,8	96,4 - 100,0	26,3	16,6 - 36	12,5	5,2 - 19,8	30,0	24,0; 42,0	24,0 - 30,0
p the level of differences according to χ2 based on the generalized log-rank test									*0,009*
Immediate results of combined treatment									
full regression	98,1	94,5 - 99,7	87,0	78,0 – 96,0	79,6	68,9 - 90,3	56,0	n/d	18,0 – 60,0
partial regression	97,7	93,2 - 98,9	25,0	16,7 - 33,3	5,76	1,3 - 10,2	30,0	24,0; 36,0	24,0 - 48,0
stabilization	82,6	67,1 - 98,1	4,4	-4,0 - 12,7	n/d	n/d	18,0	18,0; 30,0	18,0 - 48,0
p the level of differences according to χ2 based on the generalized log-rank test									*<0,001*
Reaction with $p16^{INK4}$ tumor suppressor (n=64)									
negative	33,3	-20,0 - 86,6	n/d	n/d	n/d	n/d	18,0	18,0; n/d	18,0 - 30,0
available	n/d	n/d	33,3	2,5 - 64,1	n/d	n/d	30,0	24,0; n/d	24,0 - 30,0
p the level of disagreement by the log-rank test									*0,134*

Note. n/d – not defined.

Table 5. Cox proportional hazards regression model of the influence of independent prognostic factors on the survival of patients with malignant neoplasms of the oral part of the pharynx.

Factors	Regression coefficient β	Standard error β	χ^2 Valda	p-value χ^2 Valda	RR	95 % CI
Direct results of treatment in the form of tumor growth progression (x_1)	0,932	0,145	41,16	*p<0,001*	3,72	2,78 – 5,0
Age (**x_2**)	0,018	0,009	3,86	*0,037*	1,17	1,07 - 1,46
N stage (**x_3**)	0,184	0,028	2,55	*0,049*	1,38	1,06 - 1,78

CI 36, 6 - 54.4) and 31.2% (95% CI 22.9 - 39.5), while in those of over 65 - the figures are lower and make up 31.8 respectively (95% CI 20.3 – 43.4) and 9.1% (95% CI - 0.6 - 8.8), although the latter indicator did not reach a statistically significant level (95% CI included zero in the range).

Differences in the survival rate in patients with different diagnoses by ICD and, accordingly, different localization of the pathological process *(p <0.001*) were revealed (Fig. 7).

The highest survival rates are observed in localization of the tumor on the palatine tonsil - median survival is 42.0 months (95% CI 36.0 - 48.0), lower - in localization on the vallecules pharynx and on the lingual surface of the epiglottis - 30.0 months (95% 24.0 - 36.0) and the lowest – in localization on the soft palate and on the lateral and posterior wall of the oral pharynx - 24.0 months (95% 24.0 - 30.0).

Analysis of the survival of the examined patients depending on the stage of the disease showed the worst results in patients with stage IV - so three-year survival rate in the examined patients of this group was 22.7% (95% CI 13.7 - 31.7), while in patients with stage II and III - 62.5 (95% CI 29.0 - 96.0) and 55.7% (95% CI 45.4 - 66) (p <0.001) respectively. (Fig. 8).

A similar trend in the decrease in survival rate with the deterioration of the stage of the pathological process is observed in the analysis of survival by TNM classification (Fig. 9, 10).

Analysis of patient survival rate depending on the immediate results of combined treatment showed that (Fig. 11), the probability of survival is higher (*p <0,001*) during three years in patients with complete regression of the tumor - 87.0% (95% CI 78.0 - 96.0) compared with patients with partial regression - 25.0% (95% CI 16.7 - 33.3) and stabilization of the process 4.4% (95% CI -4.0 - 12.7).

Regarding the choice of treatment strategy, the analysis of survival proved the adequacy of the applied approaches, as the best survival rates were observed in case of the best short-term results of the applied combined treatment. This was also confirmed by the analysis of factors influencing the survival rate of patients through the analysis of Cox's proportional risks. Based on the results of multiple analysis of Cox's proportional intensities, a significant (*p <0.001*) proportional model was constructed with independent prognostic factors for survival of patients with malignant oropharyngeal neoplasms - age, N stage of tumor process and short-term results of combined treatment in the form of progression of tumor growth (Table 5).

The probability of the endpoint (death of the patient) according to the regression model of proportional risks of Cox is modeled as follows:

$$H(t) = H_0(t) * \exp(b_1 \times x_1 + b_2 \times x_2 + b_3 \times x_3) \quad (1)$$

where - b_1 and b_2 - regression coefficients;

x_1 and x_2 are predictor variables presented in Table 5; $H_0(t)$ is the basic danger at time t, which represents the risk of death for a patient with a value of 0 of all predictor variables.

The regression coefficients (beta weights) are the weights for each variable in the equation. Therefore, the most important factor influencing the survival rate of the examined patients from the studied ones is the direct result of treatment, then in descending order of N stage and age of the patient.

A positive regression coefficient in predictor variable of relapse means an increase in risk and, consequently, a worsening of the prognosis in its presence. That is, the prognosis of survival deteriorates with age, N stage of the disease and the progression of tumor growth.

Based on equation 1, the risk ratio is calculated by the formula:

$$\ln(H(t) / H_0(t)) = b_1 \times x_1 + b_2 \times x_2 + b_3 \times x_3$$

Hazard ratio (or risk levels) is the degree of risk associated with each variable (factor) in fixing all other variables. HR greater than 1 indicates an increased risk for patients with this characteristic; less than 1 - a reduced risk.

Survival rate of the examined patients statistically significantly reduces in case of deterioration of direct results of treatment in the form of progression of tumor growth - the adjusted hazard ratio HR = 3,72 (95% of CI 02,78 - 5,0).

DISCUSSION

Treatment of patients with oropharyngeal cancer is still multidisciplinary with the use of surgery, chemotherapy and radiation. Surgery may be an option

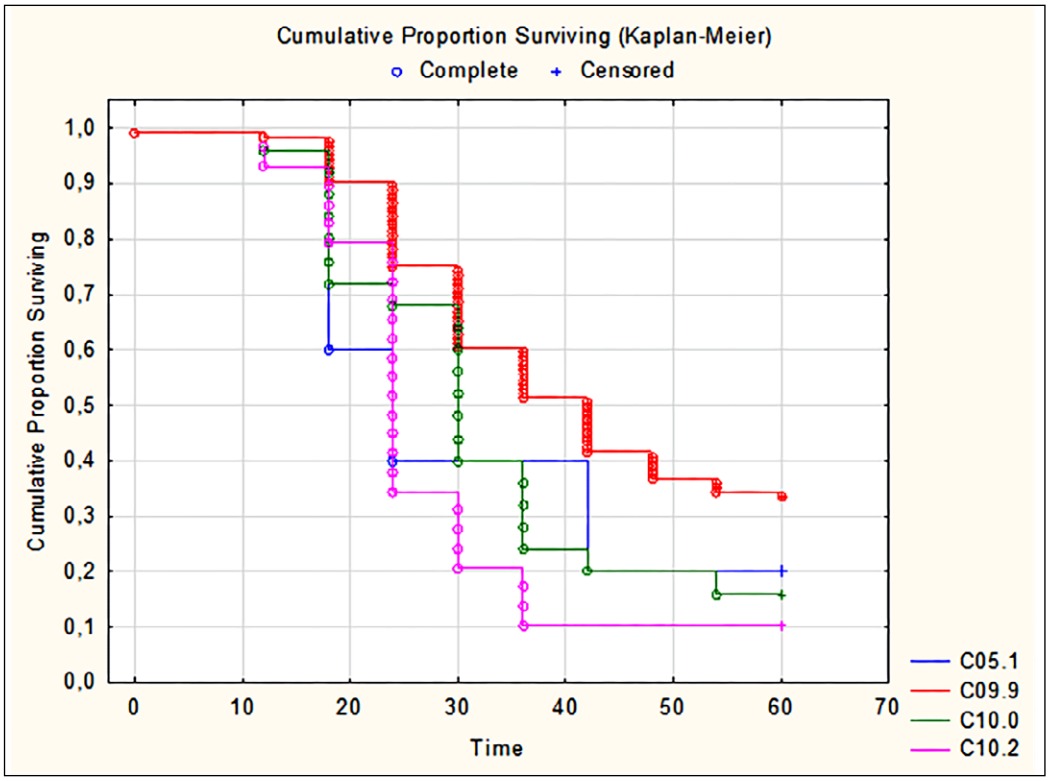

Fig. 7. Cumulative survival rate of the examined patients with oropharyngeal carcinoma depending on the diagnosis by ICD (survival period in months).

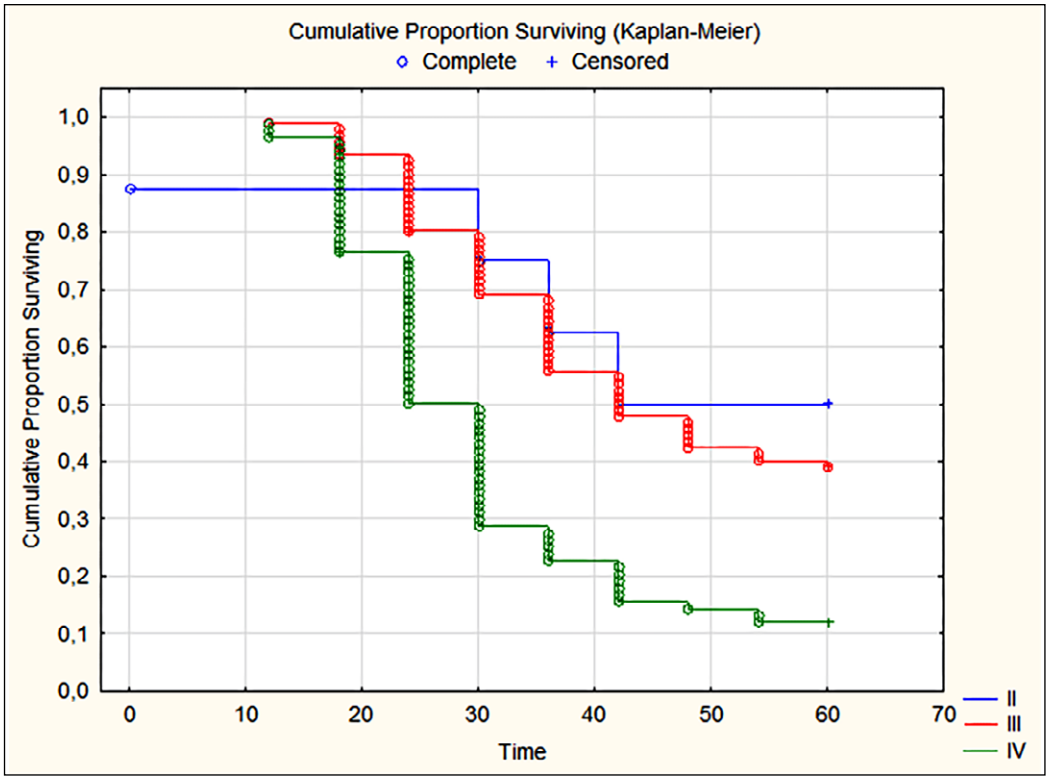

Fig. 8. Cumulative survival rate of the examined patients with oropharyngeal carcinoma depending on the disease stage (survival period in months).

for some early stages of oropharyngeal tumors. Patients with later stages of cancer or those who are inoperable usually receive radiation with or without chemotherapy.

Because toxicity is higher when chemotherapy is added, combination therapy in patients with multiple medical conditions increases the risk of treatment intolerance, which may lead to treatment interruption.

Treatment methods for cancer of head and neck tumors differ from localization in this part of the body. However, the effectiveness of primary surgical removal has been proven for tumors of the oral cavity. The protocols and tactics of laryngeal cancer treatment and their applica-

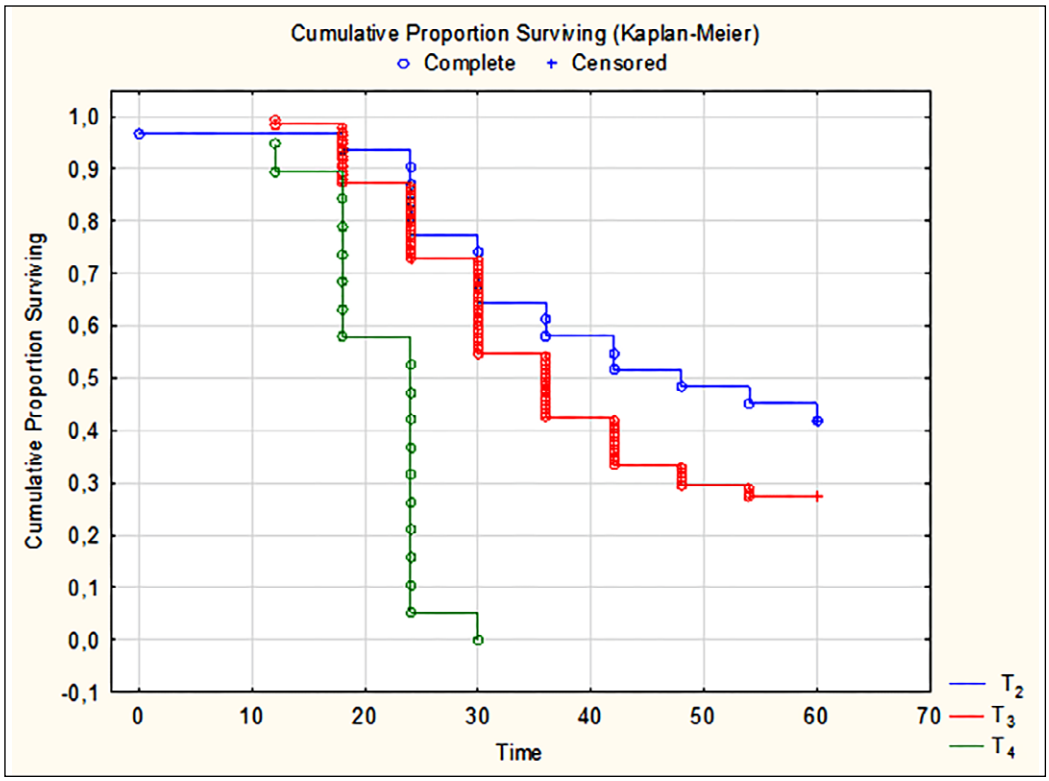

Fig. 9. Cumulative survival rate of patients examined with oropharyngeal carcinoma depending on stage of tumor process by TNM classification (tumor – T) (survival period in months).

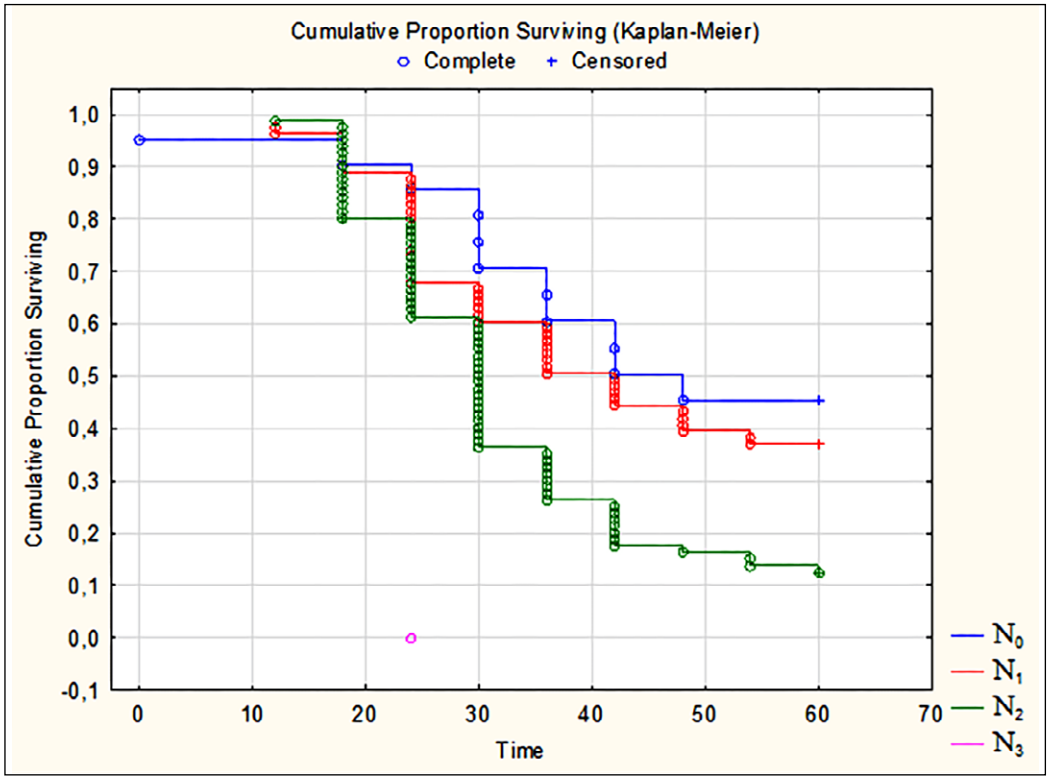

Fig. 10. Cumulative survival rate of the examined patients with oropharyngeal carcinoma depending on the stage of tumor process by TNM classification (regional lymph nodes – N)
(survival period in months).

tion in European countries provide for radiation therapy in the first stage. In the case of cancerous neoplasms of the oral part of the pharynx, meta-analyses demonstrate the usefulness of chemotherapy at the first stage.

In 2017, the staging of cancer of the oral part of the pharynx was changed depending on the association with the human papillomavirus (p16). Human papillomavirus (HPV) is detected in 20-60% of patients with oropharyngeal cancer.

The diagnosis of HPV is based on the study of its specific DNA or mRNA in a tumor cell using the polymerase chain reaction (PCR), enzyme analysis during immunohistochemical study of the p16 gene expression product - INK4A protein, or sequencing.

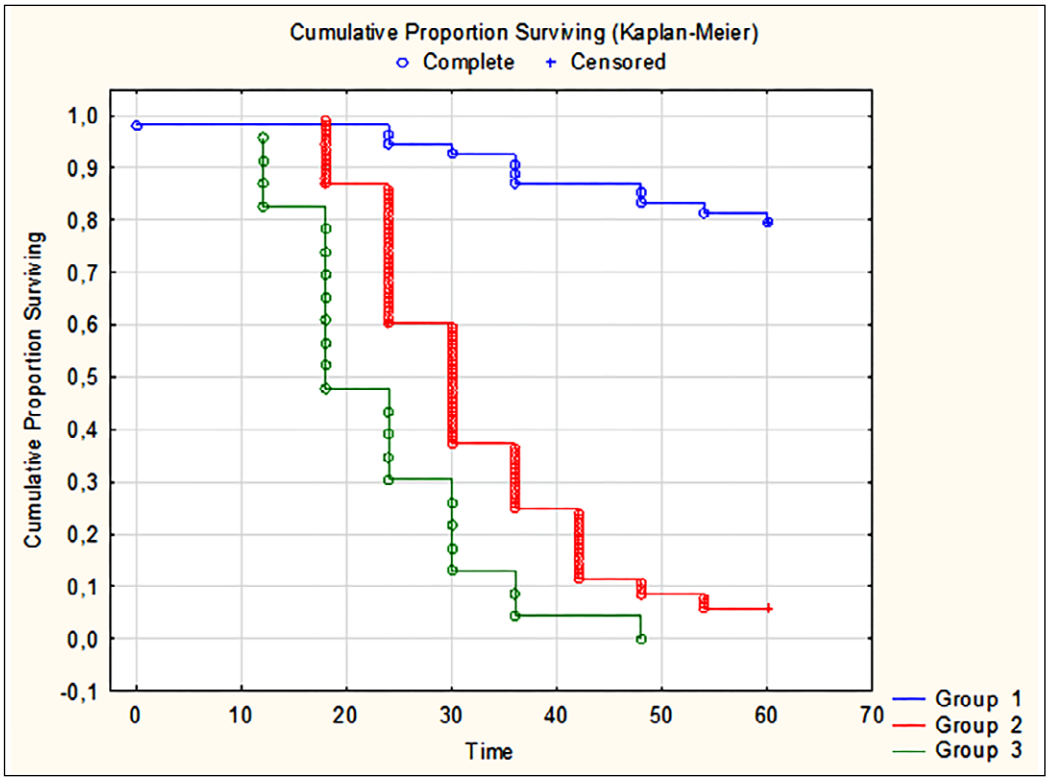

Fig. 11. Cumulative survival rate of patients with oropharyngeal carcinoma depending on short-term results of combination treatment (survival period in months)
Note. Group 1 – complete regression; Group 2 – partial regression; Group 3 – stabilization.

Overexpression of p16 protein INK4a serves as an excellent surrogate biomarker of HPV causation in oropharyngeal cancer because the early E7 protein of HPV leads to overexpression of p16 in HPV-related cancers.

In a multicenter cohort study of 7,895 patients with oropharyngeal cancer from Great Britain, Canada, Denmark, Sweden, France, Germany, the Netherlands, Switzerland, and Spain, the authors identified 4 groups of patients depending on immunohistochemical detection of p16 and HPV testing.

Thus, group 1 - patients with oropharyngeal cancer p16+/HPV– was the largest in subsites outside the tonsils and the base of the tongue (29.7% vs. 9.0%, p<0.0001). 5-year overall survival was 81·1% (95% CI 79·5–82·7).

The second group - patients with p16+/HPV+ had a 5-year survival = 40·4% (38·6–42·4).

The third group of patients with indicators - p16–/HPV–, total survival, respectively, 53·2% (46·6–60·8)

The fourth group of patients with p16–/HPV+ had a 5-year overall survival rate of 54·7% (49·2–60·9).

5-year disease-free survival for patients of the first p16+/HPV– group was 84.3% (95% CI 82.9–85.7), for the second p16+/HPV+= 60.8% (58.8–62, 9), for the third p16–/HPV–= 71·1% (64·7–8·2), for the fourth - p16–/HPV+ = respectively - 67·9% (62·5–73·7).

The study concluded that patients with discordant oropharyngeal cancer (p16–/HPV+ or p16+/HPV–) had a significantly worse prognosis than patients with p16+/HPV+ oropharyngeal cancer and a significantly better prognosis than patients with p16–/HPV– oropharyngeal cancer.

Along with routine p16 immunohistochemistry, HPV testing should be mandatory in clinical trials for all patients (or at least after a positive p16 test result). This is recommended if the HPV status may affect the treatment of patients [13].

These interesting data of the latest study, which indicate the presence of 4 groups of patients with squamous cell carcinoma of the oropharynx (SCCOPH) with different survival results depending on the detection of HPV by two different methods, can be used by clinicians in the future for more effective treatment.

Today, according to the protocols, the treatment of patients with oropharyngeal cancer (SCCOPH) is prescribed depending on the detection of the human papilloma virus.

For patients with cancerous neoplasms of the oral part of the pharynx, the meta-analyses discussed below demonstrate the usefulness of chemotherapy at the first stage.

Thus, in the MACH-NC 5872 meta-analysis, the treatment of head and neck cancer patients with the use of chemotherapy was considered. Individual data of 16,192 patients with an average follow-up period of 5.6 years were analyzed. The benefit of chemotherapy was similar for all head and neck tumor sites, with a hazard ratio for death or recurrence between 0.87 and 0.88 (p-value for interaction = 0.99). The best treatment effect was with combined chemoradiation therapy (simultaneous chemotherapy) for all tumor sites, but the test of interaction between time and treatment effect was significant only for tumors of the oropharynx

(p<0.0001) and larynx (p=0.05). The 5-year absolute effect rate associated with concomitant chemotherapy is 8.9%, 8.1%, 5.4%, and 4% for tumors of the oral cavity, oropharynx, larynx, and hypopharynx, respectively [14].

Other authors also conducted a meta-analysis of 87 trials of 16,485 treatment trials for head and neck cancer. Most patients received concomitant chemotherapy. The hazard ratio for death or recurrence was 0.88 (p<0.0001) with an absolute advantage for chemotherapy of 4.5% at 5 years and a significant interaction (p<0.0001) between time of chemotherapy (adjuvant, induction or concomitant) and treatment . Both direct (6 studies) and indirect comparison showed a more pronounced effectiveness of combined care with induction chemotherapy. For 50 related studies, the hazard ratio for death or recurrence was 0.81 (p<0.0001), and the absolute incidence was 6.5% at 5 years. There was a decrease in the effect of chemotherapy with age (p=0.003, test for trend). The authors conclude that when using concomitant chemotherapy was confirmed and was greater than from induction chemotherapy [15].

Somewhat better than our results of survival are reported by Ukrainian authors in patients with stage III-IV cancer of the oral cavity who received induction chemotherapy followed by radiation therapy. With the TPF scheme (docetaxel or paclitaxel + cisplatin + 5 fluorouracil), the 3- and 5-year survival rates were 51.4% and 42.6%, respectively.[16]

Three-year survival in patients with oral cavity and oropharyngeal cancer stage III-IV with the use of taxane-polyplatylene in the neoadjuvant regimen in another study was 40%, and with induction polychemotherapy with cisplatin - 5.3% [17] .

Our analysis of the treatment of 276 patients with cancer of the oral part of the pharynx with the use of neoadjuvant chemotherapy showed its good effectiveness despite the large number of patients with neglected stages (94%) and the presence of metastases in the lymph nodes of the neck (89.9%). Despite the fact that chemotherapy is ineffective for the treatment of metastases, we observed complete regression of regional metastases in 15% of cases.

The analysis of the survival rate of the examined patients depending on the stage of the disease showed the worst results in patients of stage IV - for example, the three-year survival rate of the examined patients of this group was 22.7% (95% CI 13.7 - 31.7), while in patients of II and III stages, respectively, 62.5 (95% CI 29.0 – 96.0) and 55.7% (95% CI 45.4 – 66) (p<0.001).

The highest survival rates are observed when the tumor is located on the palatine tonsil - median survival 42.0 months (95% CI 36.0 - 48.0), lower - when the tumor is located on the valeculus and on the lingual surface of the epiglottis - 30.0 months (95% 24 .0 - 36.0) and names when located on the soft palate and localization on the side and back wall of the oropharynx - 24.0 months (95% 24.0 - 30.0).

Diverse data on 3- and 5-year survival rates, risk ratio of death or recurrence, median survival value) in meta-analyses and articles by foreign and domestic authors indicate a considerable range of treatment schemes for oropharyngeal cancer and require further study.

Thus, the scientific goal of our work has been achieved, the dependence of the treatment results on the localization of the tumor in the oropharynx, association with the human papillomavirus, age, gender, and response of the tumor (full or partial) after primary chemotherapy has been proven. The results of the work are original for characterizing the treatment of oropharyngeal cancer patients in Ukraine.

The scientific goal was achieved, to the dependence of treatment results on the localization of relapse in the oropharynx, association with the human papillomavirus, age, gender and compliance shown (full or partial) after primary chemotherapy. The results of the work are original for the characteristics of the treatment of oropharyngeal cancer patients in Ukraine.

CONCLUSIONS

Studies of patients with malignant oropharyngeal neoplasms in which squamous cell carcinoma (90.6%) predominated, localized mainly in the palatine tonsil (73.2%), with the most frequent stages $T_3N_1M_0$ (30.1%) and $T_3N_1M_0$ %), with regional metastases to the lymph nodes of the neck (89.9%), showed that the effectiveness of treatment and rehabilitation of patients is quite high, as in most examined in the short term after combined treatment there was a complete or partial regression of the tumor (91.7%), no progression of the oncological process was detected.

In the presence of a reaction with the tumor suppressor $p16^{INK4}$, the chances of achieving complete regression of the tumor increase by 4.2 times compared to its absence (OR = 4.2; *p = 0.010*).

It was determined that with complete and partial tumor regression, a more positive reaction in patients associated with the human papilloma virus (P16 +) with the biomarker $p16^{INK4}$ (r_s = 0.33; *p = 0.007*), which can be used for screening diagnostic purposes as for tumor regression, but has a medium prognostic ability to predict complete regression.

The annual, three- and five-year survival rates of the examined patients with malignant oropharyngeal neoplasms after treatment were 97.3%, respectively

(95% CI 94.9 - 99.7); 40.8% (95% CI 33.7 - 47.9) and 27.0% (95% CI 20.6 - 33.4) with a median survival of 36 months with 95% CI (35.5 – 40.2).

Survival analysis proved the adequacy of the applied approaches to the management of patients, as the highest survival rates were observed at complete regression of the tumor - median survival of 56.0 months (95% CI 18.0 - 60.0) compared to patients with partial regression - 30.0 months (95% CI 24.0 - 48.0) and process stabilization - 18.0 months (95% CI 18.0 - 48.0) ($p<0.001$).

The effectiveness of the applied approaches is also indicated by the fact that in the direct results of combined treatment in the form of progression of tumor growth, survival rate decreases by 3.72 times (95% CI 02.78 - 5.0) and vice versa, if tumor regression is achieved - it significantly increases ($p<0,001$).

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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