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Efficacy of neoadjuvant chemotherapy with docetaxel and cisplatin in patients with squamous cell carcinoma of the oral cavity at high risk of progression

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Introduction. The question of the advisability of neoadjuvant chemotherapy (NACT) in patients with oral cavity squamous cell carcinoma is still controversial.
Aim. To identify a group of patients at high risk of progression and death from the oral cavity squamous cell carcinoma, with resectable stages, and to determine the effectiveness of docetaxel and cisplatin (TP) NACT patients with high-risk oral cavity squamous cell carcinoma.
Materials and methods. At the 1st stage of our study, we retrospectively analyzed the data of 98 patients and determine that the NACT for patients with oral cavity squamous cell carcinoma, with 3 or more factors of an unfavorable prognosis (peripheral blood parameters indicating the presence of systemic inflammation, reduced level of infiltration of tumor structures by CD8-tumor infiltrating lymphocytes and low expression of programmed death-ligand 1 (PD-L1) on tumor and immune cells) significantly reduces the risk of death and disease progression: hazard ratio 0.33; 95 % confidence interval 0.13–0.86; $p = 0.0231$. In 2nd part of study we assessed the effectiveness of 3 cycles of NACT with docetaxel + cisplatin in 24 patients with 4 or more unfavorable prognosis factors.
Results. Objective response rate after 3 cycles of NACT was 66.7 % (16/24): 1/24 (4.2 %) patient had complete response, and 15/24 (62.5 %) patients had a partial response. NACT allowed achieving disease control rate in a significant majority of patients – 23/24 (95.9 %) (p <0.001). The medians of overall survival and progression-free survival weren't reached at the time of the data cutoff (with a median follow-up of 56.5 months).
Conclusion. Our study allows to conclude that it is necessary in real clinical practice to identify patients with oral cavity squamous cell carcinoma with high-risk of progression and death in order to prescribe them NACT before surgery to increase the effectiveness of treatment and reduce the risk of progression and.

Keywords: squamous cell carcinoma of the oral mucosa, neoadjuvant chemotherapy, docetaxel, cisplatin, objective response

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Эффективность неоадъювантной химиотерапии доцетакселом и цисплатином у пациентов с плоскоклеточным раком слизистой оболочки полости рта группы высокого риска рецидива

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Введение. Вопрос о целесообразности проведения неоадъювантной химиотерапии (НАХТ) у пациентов с плоскоклеточным раком слизистой оболочки полости рта до сих пор остается спорным.
Цель исследования – выявить группу пациентов с плоскоклеточным раком полости рта с высоким риском прогрессирования и смерти на резектабельных стадиях и определить эффективность доцетаксела и цисплатина (ТР).
Материалы и методы. На 1-м этапе исследования мы ретроспективно проанализировали данные 98 пациентов и определили, что проведение НАХТ у больных плоскоклеточным раком слизистой оболочки полости рта при наличии 3 и более факторов неблагоприятного прогноза (показатели периферической крови, свидетельствующие о наличии системного воспаления, сниженный уровень инфильтрации опухолевых структур CD8-опухолевыми инфильтрирующими лимфоцитами и низкая экспрессия лиганда программируемой клеточной гибели 1 (PD-L1) на опухолевых и иммунных клетках) значительно снижает риск смерти и прогрессирования заболевания: отношение рисков 0,33; 95 % доверительный интервал 0,13–0,86; $p = 0,0231$. На 2-м этапе исследования мы оценили эффективность 3 циклов НАХТ по схеме доцетаксел + цисплатин у 24 пациентов с наличием 4 и более факторов неблагоприятного прогноза.
Результаты. Частота объективного ответа после 3 циклов НАХТ составила 66,7 % (16/24): у 1 (4,2 %) из 24 пациентов наблюдался полный ответ, у 15 (62,5 %) – частичный ответ, у 16 (66,7 %) – объективный ответ. НАХТ позволила достичь частоты контроля над заболеванием в большинстве случаев (23/24; 95,9 %) (p <0,001). Медианы общей выживаемости и выживаемости без прогрессирования не были достигнуты на момент прекращения сбора данных (при медиане наблюдения 56,5 мес).
Заключение. Результаты исследования позволяют сделать вывод о необходимости выявления в реальной клинической практике больных плоскоклеточным раком полости рта группы высокого риска прогрессирования заболевания с целью назначения им НАХТ перед операцией для повышения эффективности лечения и снижения риска прогрессирования заболевания или смерти.

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Introduction

The question of the advisability of neoadjuvant polychemotherapy in patients with oral cavity squamous cell carcinoma is still controversial. On the one hand, we remember the study by M.G. Ghi et al., which showed that induction polychemotherapy allows achieving a significant increase in overall survival (OS) (hazard ratio (HR) 0.74; 95 % confidence interval (CI) 0.56–0.97; $p = 0.031$) [1]. However, in the study, all patients received only chemoradiation therapy: none of the patients with oral cancer were operated on (and there were about 20 % of them in each group). On the other hand, a meta-analysis of 107 randomized (19,805 patients) presented by B. Lacas et al. in 2021 clearly tells us that neoadjuvant chemotherapy (NACT) does not improve OS rates (HR 0.96; 95 % CI 0.90–1.01; $p = 0.14$). But this analysis did not include patients with squamous cell carcinoma of the oral mucosa, for whom surgical treatment was the main treatment method [2]. Back in 2012, L.P. Zhong et al. presented the results of a prospective phase 3 study, which included 256 patients with stages III–IVA oral mucosal cancer: 128 patients received 2 cycles of NACT in the TPF mode. In the overall cohort of patients, NACT did not increase the OS and progression-free survival (PFS) rates, but in the group of patients with an objective response (80.6 %) or significant pathomorphological response (27.7 %), OS, locoregional control, and survival without distant metastases were significantly higher, which, in turn, indicates a unique prognostic role of NACT [3].

Currently, we are receiving more and more data from real clinical practice regarding the issue of effective NACT in patients with oral mucosal lesions. Thus, in the study by C.-L. Hsu et al. (Taiwan, 2024), during a retrospective analysis of data from 4715 operated patients with stage I–IVA squamous cell carcinoma of the oral mucosa, 815 of whom received NACT, no significant differences were obtained between the groups in terms of survival rates. But, it is noteworthy that in patients with cT2–3, cN1 and clinical stage II disease in the NACT group with subsequent surgery, the probability of achieving pT0–1 status was significantly higher (p <0.05), which allows us to think about the fact that NACT can be a kind of marker of the response to complex therapy in general [4].

M. Agrawal et al. retrospectively analyzed the data of 69 patients with "conditionally resectable" oral tumors who received NACT followed by surgery and adjuvant treatment. After NACT, the primary lesion and regional

lymph nodes became respectable in all patients, but after surgical treatment of pure cancer, resection was achieved only in 42 %. In 85.4 % of patients with primary tumor location in the tongue area, surgery was performed to a lesser extent than planned before NACT. In 30.4 %, the pathological stage was ypT0 and in 17.4 % ypN0 [5].

In a phase II study, D. Chaukar et al. compared the frequency of mandible preservation after NACT: 68 patients with oral cavity squamous cell carcinoma with clinical stage cT2–4 and cN0/N+, M0, who were indicated for resection of the mandible with disruption of its continuity, were randomized into 2 groups of 34 patients each. Group 1 received 2 cycles of NACT with docetaxel, cisplatin and 5-fluorouracil before surgery, patients of the group 2 were operated on at the I stage of treatment. In 16 of 34 patients in the NACT group (46.7 %), it was possible to preserve the continuity of the mandible. But in this study, survival rates were identical regardless of NACT [6].

Now, of course, it is impossible to claim that after NACT, in case of achieving an objective response, we can reduce the scope of surgical intervention or convert an unresectable tumor into a resectable one. We say that NACT allows for consolidation of tumor foci (due to achieving a partial or complete response) before surgical intervention, which should be carried out in the volume that was determined in the primary diagnosis, except for cases of progression against the background of NACT, when the scope of surgical intervention will have to be further increased. But we should not forget that any antitumor drug therapy is quite toxic. Thus, in the study by D. Chaukar et al., the level of toxicity in the NACT group was quite high: grade 3 was registered in 41.2 % of patients, grade 4–32.4 %) [6].

Such a high level of toxicity makes one constantly think about the issue of de-escalation of chemotherapy treatment before radical surgery or a course of radiation (chemoradiation) treatment. One of the options for de-escalation is NACT with a combination of docetaxel and cislpatin (TP regimen), without daily infusions of 5-fluorouracil. For example, in 2016, V. Narohna et al. presented data from a pilot study on the effectiveness of 3 cycles of docetaxel and cisplatin with locally advanced head and neck cancer. of the 26 patients included in the study, 65.4 % achieved an objective response after NACT, with a fairly low level of grade 3–4 adverse events (AEs) (from 15.4 to 19.2 %) [7]. Similar data were obtained in the studies of H.-Y. Tao et al. [8], L.V. Bolotina et al. [9]. And L.C. Herman et al. in 2014 proposed using a combination of paclitaxel and carboplatin as induction chemotherapy, which, according to their data, allows achieving a higher level of locoregional control (HR 0.32; $p = 0.0002$) and PFS (HR 0.57; $p = 0.02$) with no differences in OS. This regimen has significant hematological (neutropenia) toxicity: 23.3 % *versus* 7.5 %), and the TPF regimen causes significant nephrotoxicity: 15.1 % *versus* 1.6 %), which can limit the implementation of subsequent stages of antitumor treatment [10].

Thus, the aim of our study was t identification of a group of patients at high risk of progression and death from squamous cell carcinoma of the oral mucosa, with resectable stages of the disease, and to determine the effectiveness of NACT in TP regime in patients with high-risk oral cavity squamous cell carcinoma.

Materials and methods

To achieve the stated goal, we conducted a retrospective analysis and a prospective study.

Retrospective study. At the 1st stage of our study, we retrospectively analyzed the data of 98 patients with verified squamous cell carcinoma of the oral mucosa, who received treatment at the City Clinical Oncology Dispensary (Saint Petersburg) from 2010 to 2019.

The studied cohort of patients with verified oral cavity squamous cell carcinoma included 65 (66.33 %) men and 33 (33.67 %) women. The age of patients ranged from 25 to 84 years, the average age was 60.34 ± 10.86 years (95 % CI 58.16–62.51).

Most patients (51 %) were initially diagnosed with stage IVA of the disease, 14.3 % with stage III, stages I and II were diagnosed in 26.5 % of patients, and 8.16 % of patients were initially assessed as stage IVB. No distant metastases were registered in all patients included in the analysis (M0). In 47.96 % of cases, the primary tumor lesion was localized in the anterior and middle thirds of the tongue, in 25.51 % of patients, the primary tumor lesion was localized in the mucous membrane of the floor of the mouth. Lesions in other parts of the mouth were significantly less common. Morphological examination revealed a high (41.84 %) and moderate (32.65 %) degree of differentiation of oral cavity squamous cell carcinoma in most patients, with keratinization present in 43.88 % of cases.

Prospective study. As part of the 2nd stage, we conducted a prospective open phase II study to evaluate the efficacy of NACT in the TP regimen in patients with oral cavity squamous cell carcinoma with unfavorable factors identified in the first stage of the study, who received treatment and observation at the Saint Petersburg City Clinical Oncology Dispensary and in the Pavlov University. The primary endpoint of the study was the achievement of an objective response to NACT. Secondary endpoints were OS (calculated from the time of initial diagnosis to the time of death from any cause) and PFS (calculated from the start of the I stage of treatment to the time of disease progression).

We chose a single-stage Simon's design [11]. The null hypothesis (H0) was that the objective response rate (ORR) would not exceed 35 %. The numbers of patient's group was calculated using PASS v.11.0 software taking a = 0.05 and a power (β) = 0.9. The alternative hypothesis (H1) of a 65 % ORR to NACT. The study requires the inclusion of 24 patients. If 14 of them have an ORR (complete response or partial response), the H0 will be rejected.

All patients in the main group received 3 cycles of NACT in the TP regimen: docetaxel 75 mg/m^2 intravenously, and cisplatin 75 mg/m^2 intravenously, once every 21 days. The general characteristics of the patients included in the study are presented in table 1.

Table 1. *Characteristics of patients included in the study and patients in the conditional control group (n = 24)*

Parameter	Main group (neoadjuvant chemotherapy), *n* (%)
Gender: men women	 14 (58.3) 10 (41.7)
Age, years: mean, SD ± standard deviation (95 % confidence interval) min–max	 54.0 ± 10.5 (49.6–58.4) 25–73
Stage: I (T1N0M0) II (T2N0M0) III (T1N1M0, T2N1M0, T3N0M0, T3N1M0) IVA (T1N2M0, T2N2M0, T3N2M0, T4aN0-2M0)	 0 (0) 6 (25.0) 4 (16.7) 14 (58.3)
Primary lesion: tongue (anterior/middle third) floor of the oral cavity alveolar part of the mandible cheek alveolar process of maxilla	12 (50.0) 5 (20.8) 3 (12.5) 3 (12.5) 1 (4.2)
Differentiation: grade 1 grade 2 grade 3 not determined	 11 (45.8) 8 (33.3) 2 (8.3) 3 (12.5)
Keratinization: with keratinization without keratinization not determined	 16 (66.7) 4 (16.7) 4 (16.7)

The main group included 24 patients: 14 (58.3 %) men and 10 (41.7 %) women aged 25 to 73 years, the mean age was 54.0 ± 10.5 years (95 % CI 49.6–58.4). At the time of primary diagnosis of squamous cell carcinoma of the oral mucosa, most patients had stage IVA of the disease (14/24 (58.3 %); $p = 0.019$), location of the primary lesion in the lateral surface of the anterior or middle parts of the tongue (12/24 (50.04); $p = 0.034$), high (11/24 (45.8 %)) or moderate (8/24 (33.3 %)) grade of differentiation ($p < 0.001$) with the presence of keratinization (16/24 (66.7 %); $p = 0.014$).

To analyze survival, we formed a parallel (conditional control) group of patients with oral cavity squamous cell carcinoma of stages I–IVA of the disease, who did not undergo NACT, and the treatment began with the surgical stage. In the conditional control group, 16 included patients (12 (75 %) men and 4 (25 %) women) were slightly older (the average age was 62.9 ± 7.6 years (95 % CI 57.8–65.9; $p = 0.014$), with prevailing earlier stages of the disease ($p < 0.001$). Otherwise, both groups were comparable in other clinical and morphological characteristics. The median number of unfavorable factors in patients of both groups was 3 (2.0–5.5).

Results

Retrospective study. We selected the following factors identified in previous studies as factors of unfavorable prognosis for the course of the disease [12–15]. Additional factors of unfavorable prognosis are presented in table 2.

Table 2. *Factors of unfavorable prognosis of the oral cavity squamous cell carcinoma*

Parameter	Optimal cut-off
Stage	III–IVA
Peripheral blood counts (baseline visit): monocytes, % neutrophil to lymphocyte ratio (NLR) white blood cells, ×10^9/l lymphocyte, ×10^9/l eosinophil, ×10^9/l	>6.96 >2.30 ≤5.23 ≤2.88 ≤0.09
Tumor microenvironment, cells/mm^2: neutrophil, total (tumor and microenvironment) neutrophil (microenvironment) eosinophil (tumor) CD8-TIL, total (tumor and microenvironment) CD8-TIL (tumor) CD8-TIL (microenvironment)	 >39 >38 ≤1 ≤143 ≤48 ≤87
PD-L1 expression, %: PD-L1 (immune cells) PD-L1 (tumor cells)	 ≤7 ≤15

Note. *TIL – tumor infiltrating lymphocytes; PD-L1 – programmed death-ligand 1.*

Using ROC analysis and Youden's index, the optimal threshold value of the number of unfavorable prognosis factors was determined, which was 3: the presence of 4 or more unfavorable factors in a patient significantly worsens the prognosis of the disease ($p < 0.0001$).

In order to determine the group of patients with an unfavorable prognosis of the disease, we performed a multivariate analysis by constructing a Cox proportional hazards model using the Wald sequential exclusion method, which included the following indicators:

- stage;
- number of unfavorable prognosis factors from table 1;
- surgical treatment;
- lymphadenectomy;

- NACT;
- adjuvant radiotherapy.

The constructed model was statistically significant (p <0.0001), with good quality (Harrel's C-index = 0.790; 95 % CI 0.724–0.855). According to the analysis, the final model included the stage of the tumor process, the number of unfavorable factors (according to table 1), and the implementation of NACT followed by surgical intervention. Adjuvant radiotherapy and cervical lymph node dissection did not affect the OS of patients and were excluded from the model. The results of the analysis with the construction of Cox regression are presented in table 3.

Table 3. *Multivariate analysis in patients with oral cavity squamous cell carcinoma*

Parameter	Hazzard ratio	95 % confidence interval	*p*-value (Cox regression)
Stage of disease >II	1.34	0.87–2.04	0.1805
Number of unfavorable prognosis factors >3	1.21	1.05–1.40	0.0096
Surgical treatment was conducted	0.13	0.05–0.33	<0.0001
Neoadjuvant chemotherapy was conducted	0.33	0.13–0.86	0.0231

In the final model, only the stage of the tumor process did not have a significant effect on the OS of patients: p = 0.1805; HR 1.34; 95 % CI 0.87–2.04. All other factors significantly affected the course and outcome of the disease.

During the study, we were able to determine that the implementation of NACT in those patients with oral cavity squamous cell carcinoma who have >3 factors of an unfavorable prognosis for the course of the disease significantly reduces the risk of death of patients and disease progression: HR = 0.33; 95 % CI 0.13–0.86; p = 0.0231.

Prospective study. After completion 3 cycles of NACT, all patients underwent control CT of the maxillofacial region, soft tissues of the neck and chest. The response to therapy was assessed according to Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1). The overall response is presented in table 4.

We achieved the primary endpoint of the study – the objective response rate after 3 cycles of NACT was 66.7 % (16/24): 1 (4.2 %) patient had a complete tumor response to therapy, and 15 (62.5 %) patients had a partial response. Tumor stabilization was achieved in 7/24 (29.2 %) patients. Thus, NACT allowed achieving disease control in a significant majority of patients – 23/24 (95.9 %) (p <0.001). Only 1 (4.2 %) patient experienced tumor progression during induction therapy, but the tumor still remained resectable.

As part of the 2nd stage of complex treatment, all patients of the main group underwent radical surgery. The question of the need and volume of adjuvant treatment was decided upon receiving the results of the postoperative morphological report: in the presence of unfavorable pathomorphological factors, according to the current clinical recommendations, patients underwent adjuvant therapy based on radiation therapy. The general characteristics of surgical and adjuvant treatment are presented in table 5.

Table 4. *Response of tumor foci to induction chemotherapy according to Response Evaluation Criteria in Solid Tumors 1.1 (n = 24)*

Parameter	Main group (neoadjuvant chemotherapy), *n* (%)
Complete response (CR)	1 (4.2)
Partial response (PR)	15 (62.5)
Objective response rate (OOR) (CR + PR)	16 (66.7)
Stable disease (SD)	7 (29.2)
Disease control rate (OOR + SD)	23 (95.9)
Progression	1 (4.2)

Table 5. *Surgical and adjuvant treatment of patients with oral cavity squamous cell carcinoma (n = 24)*

Parameter	Main group (neoadjuvant chemotherapy), *n* (%)
Surgical treatment: without reconstructive with reconstructive	 8 (33.3) 16 (67.7)
Lymph node dissection: required not required	 20 (83.3) 4 (16.7)
Postoperative radiation therapy: required not required	 19 (79.2) 5 (20.8)

The majority of patients in the main group 16/24 (67.7 %) underwent extended combined surgery with a reconstructive (p = 0.017), with cervical lymph node dissection 20/24 (83.3 %) (p <0.001). Adjuvant radiotherapy was received by 19/24 patients (p <0.001). In the conditional control group, the frequency of surgical interventions with a reconstructive was comparable (p = 0.199).

Considering the fact that any antitumor therapy is aimed at increasing the life expectancy of patients and increasing the period without disease progression, at the next stage of our study we compared the OS and PFS rates in the main and conditional control groups of patients. The results of the survival analysis are presented in fig. 1 and 2.

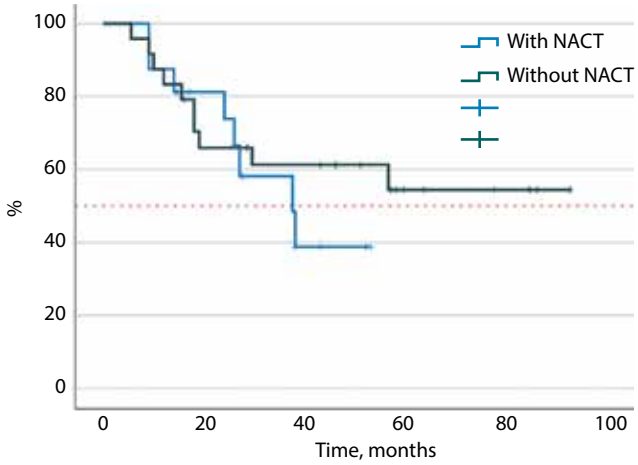

Fig. 1. *Overall survival of patients with oral cavity oral cavity squamous cell carcinoma depending on neoadjuvant chemotherapy (NACT)*

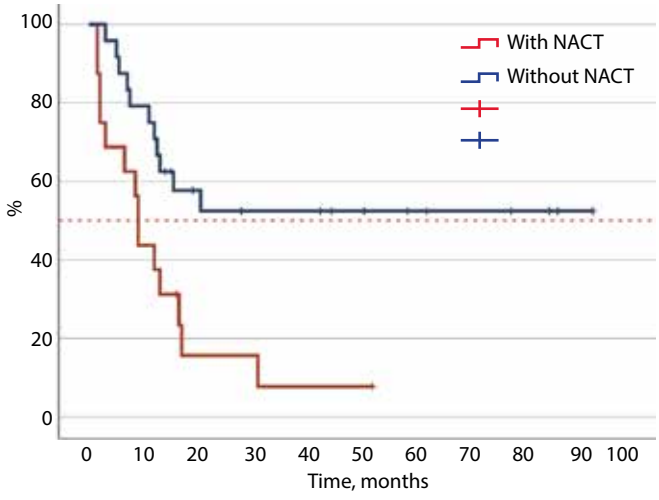

Fig. 2. *Progression-free time in patients with oral cavity squamous cell carcinoma depending on neoadjuvant chemotherapy (NACT)*

The median OS in patients of the main group at the time of the data cutoff was not reached (with a median follow-up of 56.5 months). The median OS of patients of the conditional control group who did not receive NACT was 37.5 months (95 % CI 21.7–53.3). When comparing the median OS using the Mantel–Cox log-rank test, no significant differences were found: $p = 0.430$ (relative risk 1.46; 95 % CI 0.56–3.81).

The median PFS in patients of the main group who received 3 cycles of NACT was not reached at the time of the data cut-off (with a median follow-up of 56.5 months). The median PFS in patients of the conditional control group who did not receive NACT was 9.0 months (95 % CI 8.0–10.0). When comparing the medians of PFS using the Mantel–Cox log-rank test, significant differences were obtained: $p = 0.007$ (relative risk 3.01; 95 % CI 1.36–6.70). In other words, NACT allows to reduce the risk of progression in patients with oral cavity squamous cell carcinoma by 3 times.

Discussion

Our retrospective analysis allowed us to identify a high risk group of disease recurrence and death among patients with resectable squamous cell carcinoma of the oral mucosa, which is characterized by a locally advanced stage of the disease (III–IVA), the presence of 4 or more additional factors of an unfavorable prognosis, which include peripheral blood parameters indicating the presence of systemic inflammation in the patient against the background of the developed malignant process, as well as a reduced level of infiltration of tumor structures by CD8-TIL and low expression of programmed death-ligand 1 (PD-L1) on tumor and immune cells, indicating insufficient immunogenicity of the tumor, to date, in the literature, this issue is insufficiently covered in relation to the group of patients with squamous cell carcinoma of the oral mucosa, and the results in some cases vary greatly. Our multifactorial analysis showed that NACT can significantly reduce the risks in this cohort of patients. In this regard, the conducted study of the effectiveness of NACT in the TP mode made it possible to achieve the frequency of objective response and disease control that are not inferior to the results of studies devoted to studying the effectiveness of various NACT regimens [16–19].

Conclusion

Our study allows us to conclude that it is necessary in real clinical practice to identify patients in the high-risk group of patients with oral cavity squamous cell carcinoma in order to prescribe them NACT before surgery to increase the effectiveness of treatment and reduce the risk of progression and death from the malignant process.

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