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O. BURTYN [1, *], T. BORIKUN [2], O. ROSSYLNA [3], A. KOPCHAK [4], O. KRAVETS [1]

[1] Nonprofit organization “National Cancer Institute”, Kyiv, Ukraine
[2] R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of the NASU, Kyiv, Ukraine
[3] Clinics for Personalized Diagnostics and Therapy Design “Oncotheranostics”, Kyiv, Ukraine
[4] Bogomolets National Medical University, Kyiv, Ukraine

* Correspondence: Email: olyabyrtun@gmail.com

CLINICAL SIGNIFICANCE OF SALIVARY MIR-21, -155, AND -375 IN PATIENTS WITH SQUAMOUS CELL CARCINOMA OF ORAL CAVITY

Background. The current prognostic markers in oral squamous cell carcinoma (OSCC) have limited accuracy sometimes leading to inappropriate treatment decisions. Identifying new markers would help clinicians tailor treatment plans based on the individual patient risk factors leading to improved survival rates and quality of life. **Aim.** To estimate the value of the miRNA expression indicators in saliva as prognostic and predictive markers of the effectiveness of neoadjuvant chemotherapy (NACT). **Materials and Methods.** The work is based on the results of the examination and treatment of 61 patients with stage II—IV OSCC. The miR-21, miR-155, and miR-375 expression levels in the saliva samples were analyzed by the real-time reverse transcription polymerase chain reaction. **Results**. The salivary miR-21 and -155 expression levels in healthy volunteers were 2.49 and 2.84 times lower than in OSCC patients ($p < 0.05$). The positive association of miR-21 and miR-155 expression levels and the negative correlation of miR-375 expression level with T index by TNM (r = 0.68, r = 0.75, and r = −0.67, respectively) ($p < 0.05$) and the presence of lymph node metastasis (r = 0.78, r = 0.71, and r = −0.59, respectively) ($p < 0.05$) were found. Patients with good response to NACT had lower miR-21 and -155, and higher miR-375 levels in saliva compared to those with resistant tumors. **Conclusions**. Our study suggests that salivary miR-21, miR-155, and miR-375 may be potential biomarkers for the prognosis of cancer course and the response to NACT in OSCC patients.

Keywords: OSCC, miRNA, neoadjuvant chemotherapy.

Oral squamous cell carcinoma (OSCC) is a prevalent and aggressive form of head and neck cancer, accounting for a significant portion of cancer-related morbidity and mortality worldwide [1]. Despite the advancements in treatment modalities, including surgery, radiotherapy, and chemotherapy, the prognosis for OSCC patients remains challenging, with a high rate of recurrence and poor overall survival. Current OSCC diagnosis and prognosis often rely on tissue biopsies representing an invasive procedure. This necessitates the development of more accessible and patient-friendly alternatives.

Saliva is a complex body fluid, containing a lot of regulatory molecules, similar to ones that can

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be encountered in blood. According to Roi et al. [2], cancerous cells enter the salivary flow through the gingival sulcus, transcellular (active or passive transport), or paracellular routes offering the opportunity to identify the presence of multiple specific biomarkers associated with the OSCC initiation and progression leading to locoregional metastasis.

Due to the ease of collection, saliva containing substances relevant to the physiological changes in the body has emerged as a promising source for potential biomarkers [2]. MicroRNAs (miRNAs) are small, non-coding RNAs that play crucial roles in regulating various cellular processes, including proliferation, differentiation, and apoptosis. Recent studies have highlighted the potential of miRNAs as promising biomarkers for cancer diagnosis, prognosis, and prediction of therapeutic response [3]. The aberrant miRNA expression has been implicated in the development and progression of various malignancies, including OSCC.

Except for cancer cells, other sources of salivary miRNAs are normal epithelial and immunocompetent cells. Their levels can be affected by diet and water consumption and can be population-specific due to the differences in dietary preferences [4], along with age, gender, circadian rhythm, drug intake, and environmental exposures [5]. Thus, the results of studies of the potential clinical application of salivary miRNAs should be validated on different samples and tailored to the local demographic features.

Some authors speculate that tumors and salivary miRNAs can demonstrate similar expression patterns during OSCC progression [6]. Currently, there are only a few studies aimed at identifying salivary miRNAs as predictive biomarkers, while studies devoted to miRNAs in tumor and serum are more common.

Basing on the available literature information, we selected miR-21, miR-155, and miR-375 for our studies [7—9] to explore the potential of these miRNAs as promising non-invasive biomarkers in saliva for OSCC diagnosis, prognosis, and prediction of therapy outcome. The saliva collection offers a significant advantage over traditional tissue biopsies as a non-traumatic, readily available, and cost-effective method [10]. The studies have shown that the expression levels of these miRNAs in saliva can be indicative of the presence and aggressiveness of OSCC, highlighting their potential as valuable tools for early detection and personalized treatment planning [11].

The aim of the study was to estimate the value of the miR-21, miR-155, and miR-375 expression levels in saliva as prognostic and predictive markers of the effectiveness of neoadjuvant chemotherapy (NACT) in OSCC patients.

Materials and Methods

General clinical characteristics of patients with OSCC. The study was conducted on saliva samples obtained from 61 patients with OSCC, who were treated in the Research Department of Head and Neck Cancer of the Nonprofit organization “National Cancer Institute” (NCI) of the Ministry of Health of Ukraine (Kyiv) from 2017 to 2020. Also, saliva samples (n = 10) were taken from healthy volunteers (5 males and 5 females), 55.6 ± 16.8 years old. All subjects provided informed consent on the use of their clinical data for scientific purposes and the research was approved by the Medical Ethical Committee of the NCI and was carried out in conformity with the guidelines of the Declaration of Helsinki. The general clinical and pathological characteristics of the patients are presented in Table 1.

The tumor stage was determined according to the International TNM Classification (8th edition, 2017). The histological type of tumor was established according to the WHO classification (2017).

In our study, all patients received three cycles of NACT according to the TPF regimen (intravenous docetaxel 75 mg/m^2 on day 1; intravenous cisplatin 75 mg/m^2 on day 1; intravenous 5-fluorouracil 750 mg/m^2 per day as a continuous infusion on days 1 to 4). The interval between NACT cycles was 3 weeks.

The response assessment of NACT was performed using computed tomography of the head and neck at the end of treatment according to the RECIST 1.1 criteria (Response Evaluation Criteria in Solid Tumors, 2009) [12].

The patients who had a complete tumor response following NACT received radiotherapy. Those with a partial tumor response and stable disease underwent surgery and adjuvant radiotherapy or concurrent platinum-based chemoradiotherapy. In cases where the disease progressed, surgery was performed if possible or concurrent chemoradiotherapy was considered.

Real-time PCR. The real-time reverse transcription polymerase chain reaction (RT-PCR) was used to study the expression of miR-21, miR-155, and miR-375 in saliva samples of patients with OSCC.

Total RNA was isolated from saliva samples using the commercial NucleoSpin kit (MACHEREY-NAGEL, Germany). The quantity of the isolated RNA was determined using a spectrophotometer "NanoDrop 1000 Spectrophotometer" (ThermoScientific, USA). The purity of the isolated RNA was monitored by the ratio of optical absorption values at the wavelengths of 260 and 280 nm. RNA was dissolved in Tris-EDTA buffer and stored at –20 °C until use. The RT-PCR was performed on a quantitative detection system QuantStudio 5 Dx Real-Time PCR System (ThermoScientific, USA) using a commercial kit for RT-PCR TaqMan MicroRNA Assay (ThermoScientific, USA) according to the manufacturer's protocol.

To determine miR-21-5p, we used the stem-loop primer for the synthesis of cDNA 5'- GTTGGCTCTGGTGCAGGGTCCGAGGTATTCGCACCAGAGCCAAC TCAACA-3' and for RT-PCR, forward primer was 5'- UAGCUUAUCAGACUGAUGUUGA -3'.

For miR-155-3p detection, we used stem-loop primer 5'-GTTGGCTCTGGTGCAGGGTCCGAGGTATTCGCACCAGAGCCAAC TGTTAA-3' and for RT-PCR, forward primer was 5'- GTTTGGCTCCTACATATTAGCA-3'.

For miR-375-3p detection, we used stem-loop primer 5'- GTTGGCTCTGGTGCAGGGTCCGAGGTATTCGCACCAGAGCCAAC TCACGC-3' and for RT-PCR, forward primer was 5'-GTGTTTGTTCGTTCGGCTC-3'.

According to the stem-loop miRNA RT-PCR technique, a universal reverse primer 5'-GTGCAGGGTCCGAGGT-3' was used [13]. Primer sequences for the detection of miR-21, -155, and -375 were obtained using the resource genomics.dote.hu:8080/mirnadesigntool/ and synthesized by Metabion, Germany.

RNU48 microRNA was used as an endogenous control to objectify the expression parameters. The primer sequences for RNU48 were synthesized by Metabion, Germany: forward 5'-AGTGATGATGACCCCAGGTAACTC-3' and reverse 5'-CTGCGGTGATGGCATCAG-3'. The relative expression of miR-21, miR-155, and miR-375 was determined by the comparative ΔCT method [14].

The threshold cycle was averaged in all technical and biological replicas in the middle of each line. The fold difference (fold change) between the expression of the studied miRNAs was calculated by the formula $2^{-\Delta Ct}$ (hereinafter — a.u.). The errors for the fold difference calculations show a range of ΔCt values based on the inclusion of standard deviation in these values.

Statistical analysis. Statistical processing of the obtained results was carried out using STATISTICA 6.0 program (Statistica Inc., USA). Standard descriptive, parametric, and non-parametric statistical methods were used. A comparison of the reliability of differences between the mean values was carried out using Student's *t*-test (for a parametric distribution) or the Mann — Whitney U-test (for a non-parametric distribution). The analysis of the contingency of the traits was performed using the Chi-square method. A correlation analysis was performed using Pearson and Spearman correlation coefficients for parametric and non-

Table 1. **Clinical and pathological characteristics of the patients with OSCC (n = 61)**

Index	Number of patients	
	n	%
Average age, years	57.2 ± 8.5	
Sex		
Male	44	72.0
Female	17	28.0
T category by TNM		
T2	9	14.8
T3	21	34.4
T4	31	50.8
N category by TNM		
N0	17	27.8
N1	28	46.0
N0	16	26.2
Differentiation grade, G		
G1	15	24.6
G2	38	62.3
G3	8	13.1
Stage		
II	4	6.5
III	21	34.5
IVa	36	59.0

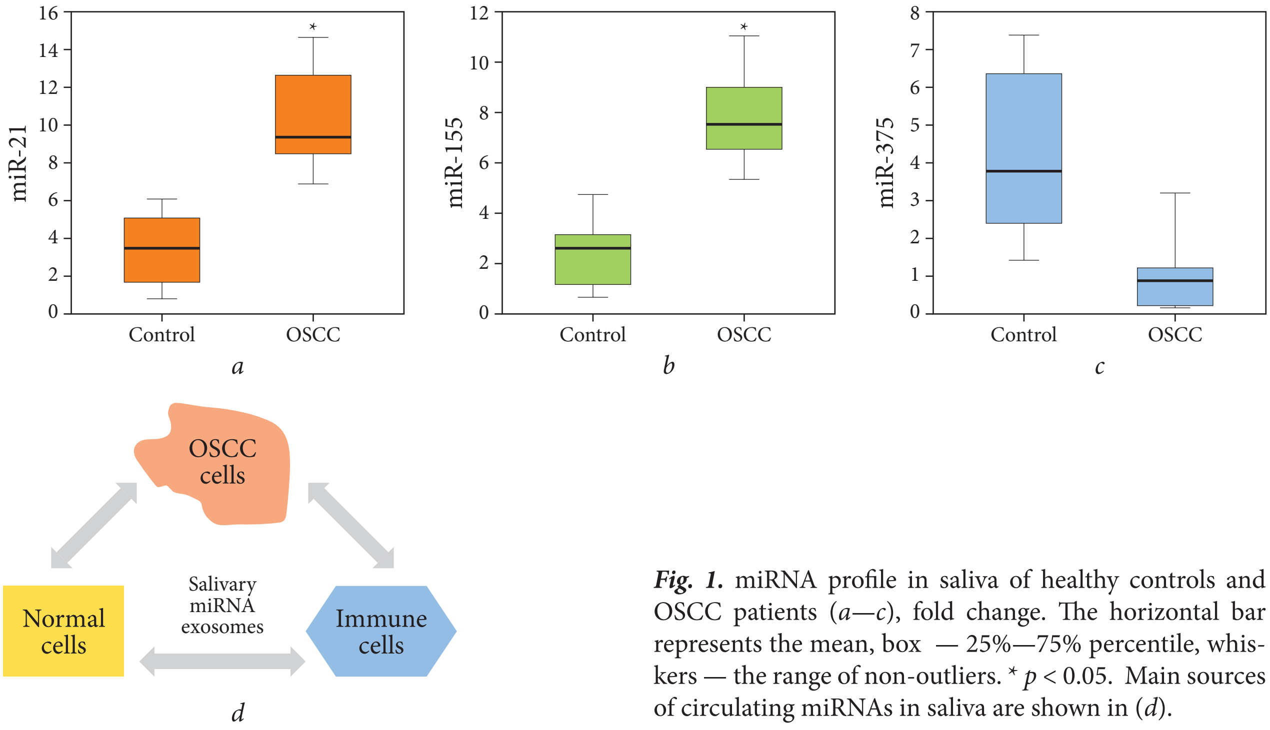

Fig. 1. miRNA profile in saliva of healthy controls and OSCC patients (*a*—*c*), fold change. The horizontal bar represents the mean, box — 25%—75% percentile, whiskers — the range of non-outliers. * $p < 0.05$. Main sources of circulating miRNAs in saliva are shown in (*d*).

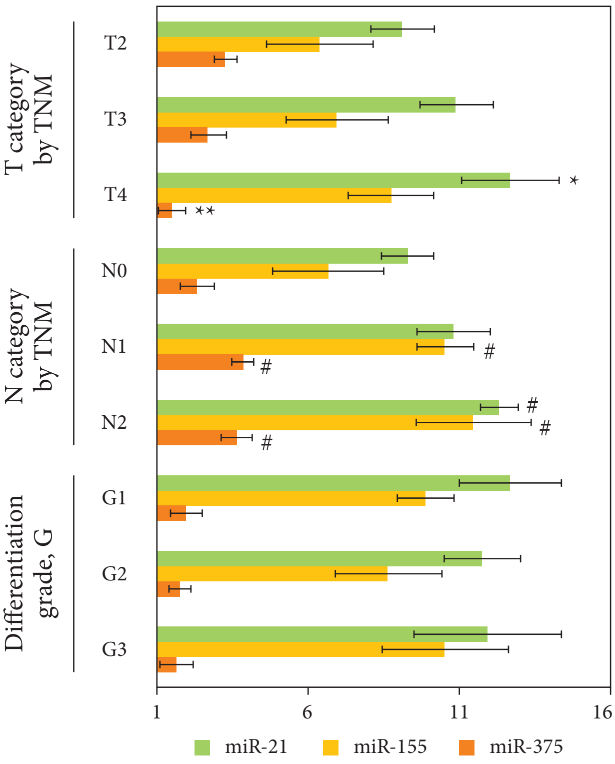

Fig. 2. Association of the salivary miR-21, miR-155, and miR-375 expression with clinical and pathological features of OSCC patients, fold change. $p \le 0.05$ compared to T1 patients; ** $p < 0.05$ compared to T1 and T2 patients; # $p < 0.05$ compared to N0 patients

parametric types of data distribution, respectively. The data are presented as M ± m, where M is the arithmetic mean; m is the standard error of the mean, or as a percentage for relative values. Differences at $p \le 0.05$ were considered significant.

Results and Discussion

We estimated the levels of miR-21, -155, and -375 in the saliva of OSCC patients before treatment and compared them with those in healthy subjects (hereinafter — control). We found that in the saliva of healthy controls, the levels of miR-21 and -155 were 2.49 and 2.84 times lower ($p < 0.05$), while miR-375 expression was 5.3 times higher than in the OSCC cases but no significant differences were established (Fig. 1).

Further analysis of the association between the clinicopathological features and miR-21, miR-155, and miR-375 levels in OSCC patients revealed that the up-regulation of miR-21 and -155 expression and down-regulation of miR-375 levels are associated with a more advanced stage of OSCC (Fig. 2).

Also, we conducted a correlation analysis of the examined miRNAs association with the clinical-pathological features of OSCC patients. Interestingly, the miR-21 and -155 levels positively correlated with the T index by TNM (r = 0.68 and r = 0.75, respectively) ($p < 0.05$), and higher levels were observed in the saliva of patients with lymph node metastases (r = 0.78 and r = 0.71, respectively) ($p < 0.05$). The expression of miR-375 negatively correlated with T by TNM (r = −0.67) ($p < 0.05$), and in patients with N1-2, its levels were 2.1 times higher than in the saliva from patients without lymph node metastases (r = −0.59).

There are scarce data on salivary miRNAs role in OSCC progression. In particular, Jadhav et al. [8] reported a statistically significant correlation between the metastatic and non-metastatic groups by miR-21 expression in saliva with a positive predictive value of up to 82%.

Di Stasio et al. [15] stated that the salivary miR-21 levels do not show any variation among groups with oral epithelial dysplasia and OSCC but at the same time, Garg et al. [16] reported that miR-21 has diagnostic potential since its levels increased in the saliva from patients with oral epithelial dysplasia and OSCC. Tu et al. [9] demonstrated that the salivary miR-375 levels decreased markedly in the patients with potentially malignant oral disorders, compared with the controls, and patients with OSCC during the follow-up period showed lower expression of salivary miR-375 than the others. Another study by Wiklund et al. [17] revealed that the aberrant miR-375 in saliva could distinguish between OSCC patients and healthy volunteers, but no further studies have been reported.

To evaluate the predictive value of the salivary miR-21, miR-155, and miR-375, we divided all patients into 2 groups depending on the clinical effect of NACT (according to RECIST criteria 1.1.). Group 1 included 38 patients with a positive response to NACT (17 (28%) complete response (CR) and 21 (34.4%) partial response (PR)). Group 2 included 23 patients with tumors resistant to the treatment (13 (21.3%) stable disease (SD) and 10 (16.3%) progressive disease (PD)). High/low microRNA expression was assessed by the median level.

Table 2. **Association between salivary miRNA expression and the NACT efficacy (Chi-square test)**

Criterion	miR-21		miR-155		miR-375	
	high	low	high	low	high	low
CR	3	12	8	8	12	3
PR	8	10	8	10	12	6
SD	14	2	9	6	5	11
PD	10	2	7	5	5	7
Sensitive	11	22	16	18	24	9
Resistant	24	4	16	11	10	18
Objective response rate	31.43	84.62	50.00	62.07	70.59	33.33
χ^2	8.279		3.894		7.975	
p	**0.004***		0.09		**0.01***	

Note: * $p < 0.05$. For CR, PR, SD, and PD, see the text.

The associations between microRNA expression and NACT response are summarized in Table 2. The analysis of miR-21, miR-155, and miR-375 depending on the response of tumors to therapy showed that only miR-21 and -375 indicators were associated with response to NACT.

In the process of the statistical processing of the obtained data in the above-mentioned cohorts of OSCC patients, we tried to optimize the further clinical application of the mentioned miRNAs. We divided patients into subgroups to find miRNA levels that allowed for the separation of at least 85% of the responders from non-responders. As seen from Table 3, the miR-21, miR-155, and miR-375 levels in saliva from 85% of OSCC cases with resistant tumors were above 10.1 and 9.8 and below 1.1 a.u., respectively, while 85% of patients with a good response to therapy were characterized by lower miR-21 (<9.2), -155 (<9.4) and higher miR-375 (>1.1) levels. Certainly, these observations are subjected to several limitations due to the relatively small sample size and the lack of data on several relevant immunological indicators. Therefore, future studies are required to validate the current findings.

There is no available experimental data on the association of salivary miR-21, miR-155, and

Table 3. **Relationship between salivary miRNA indicators and the sensitivity of OSCC to NACT**

Sensitivity	microRNA	Level, a.u.	
Sensitive	miR-21	↓	< 9.2
	mir-155	↓	< 9.4
	miR-375	↑	> 2.1
Resistant	miR-21	↑	> 10.1
	mir-155	↑	> 9.8
	miR-375	↓	< 1.1

Note: * $p < 0.05$. For CR, PR, SD, and PD, see the text.

miR-375 with OSCC response to NACT. However, elevated miR-21 levels in tumor tissue and blood serum correlated with resistance to cisplatin therapy in a variety of cancers, possibly via inhibition of pro-apoptotic proteins like PTEN and BIM [18]. miR-155 displays a complex role in OSCC. While some studies suggested that it promoted tumor growth by targeting some tumor suppressor genes (like *SOCS1*), others hinted at its potential role in activating the immune system. Several studies suggested that miR-155 overexpression might contribute to the chemoresistance in OSCC. For example, Kirave et al. [19] indicated its possible role in cisplatin resistance through the *FOXO3a*-mediated pathway.

Unlike miR-21, miR-375 exhibits anti-tumorigenic properties. Studies show that it might increase sensitivity to radiation by downregulating DNA repair enzymes and enhancing cell cycle arrest [20]. The most recent study by Huni et al. [21] revealed a tight association between miR-375 expression in OSCC cell lines and their sensitivity to cisplatin, fluorouracil, and paclitaxel. The authors assumed that miR-375 affects drug sensitivity due to a positive association with the rearranged L-myc fusion transcription factor expression in chemoresistant oral cancers [21].

Future studies should explore these microRNAs interplay with OSCC therapy response in more detail. Identifying miRNA signatures associated with positive or negative outcomes could pave the way for personalized treatment plans based on a patient's specific microRNA profile. This holds immense potential for improving treatment efficacy and patient outcomes in OSCC.

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О. Буртин [1], Т. Борікун [2], О. Россильна [3], А. Копчак [4], О. Кравець [1]
[1] Державне некомерційне підприємство «Національний інститут раку», Київ, Україна
[2] Інститут експериментальної патології, онкології і радіобіології
ім. Р.Є. Кавецького Національної академії наук України, Київ, Україна
[3] Клініка персоналізованої діагностики і дизайну терапії “Онкотераностика”, Київ, Україна
[4] Національний медичний університет імені О.О. Богомольця, Київ, Україна

КЛІНІЧНЕ ЗНАЧЕННЯ ПОКАЗНИКІВ мікроРНК-21, -155 ТА -375 У СЛИНІ ХВОРИХ НА ПЛОСКОКЛІТИННИЙ РАК РОТОВОЇ ПОРОЖНИНИ

Стан питання. Рак ротової порожнини (РРП) є поширеним видом онкологічних захворювань. Існує гостра потреба у більш точних прогностичних та предиктивних маркерах. Виявлення нових маркерів дозволить призначати лікування з урахуванням індивідуальних факторів ризику кожного пацієнта. Наявні маркери мають обмежену точність, що інколи призводить до неправильного вибору тактики лікування. Пошук нових прогностичних маркерів РРП є критично важливим для оптимізації стратегій терапії, покращення показників виживання та якості життя пацієнтів. **Мета**. Оцінка значення показників експресії мікроРНК у слині як прогностичних та предиктивних маркерів ефективності неоад’ювантної хіміотерапії (НАХТ). **Матеріали та методи**. Робота базується на результатах обстеження та лікування 61 хворого на плоскоклітинний РРП II—IV стадії, які перебували на лікуванні в науково-дослідному відділенні раку голови та шиї ДНП «Національний інститут раку». Експресію мікроРНК-21, -155 і -375 у зразках слини аналізували за допомогою зворотно транскрипційної полімеразної ланцюгової реакції в реальному часі. **Результати**. Встановлено, що у слині здорових донорів показники експресії мікроРНК-21, -155 нижчі у 2,49 та 2,84 рази ($p < 0,05$) порівняно з хворими на РРП. Ми виявили позитивну асоціацію показників мікроРНК-21, мікроРНК-155 і негативну кореляцію рівнів мікроРНК-375 з T за TNM ($r = 0,68$, $r = 0,75$ і $r = –0,67$, відповідно) ($p < 0,05$) і наявністю метастазів у лімфатичних вузлах ($r = 0,78$, $r = 0,71$ та $r = –0,59$, відповідно) ($p < 0.05$). Пацієнти з кращою відповіддю на НАХТ мали нижчі рівні мікроРНК-21 і -155 і вищі рівні мікроРНК-375 у слині порівняно з пацієнтами із резистентними пухлинами. **Висновки**. Рівні мікроРНК-21, мікроРНК-155 і мікроРНК-375 у слині можуть бути потенційними біомаркерами прогнозу перебігу та відповіді на НАХТ у пацієнтів з РРП. Проте потрібні подальші масштабні дослідження, щоб підтвердити ці висновки та більш детально вивчити їх клінічне застосування.

Ключові слова: рак ротової порожнини, мікроРНК, неоад’ювантна хіміотерапія.