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# Expression and Clinical Significance of microRNA-1246 in Human Oral Squamous Cell Carcinoma

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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**Background:** MicroRNAs (miRNAs) are small, non-coding RNAs that may function as oncogenes or tumor suppressors. Previous studies have shown that the expression level of miR-1246 was enhanced in multiple types of cancers. However, the expression of miR-1246 in human oral squamous cell carcinoma (OSCC) and its prognostic values remain unclear.

**Material/Methods:** Quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR) was used to analyze the expression of miR-1246 in 106 pairs of matched normal and tumor tissue samples. The chi-square test was used to examine the associations between miR-1246 expression and the clinicopathological characters. The survival curves were constructed by the Kaplan-Meier method. The influence of each clinical variable on survival was examined by the Cox multivariate regression analysis.

**Results:** The expression level of miR-1246 was significantly higher in tumor tissues and oral cancer cell lines than in normal controls ($p<0.01$). High expression of miR-1246 was found to significantly correlate with nodal status ($p=0.015$), TNM stage ($p=0.005$), and tumor grade ($p=0.002$). Enhanced miR-1246 correlated significantly with patient survival ($p<0.01$). In multivariate analysis, we found that miR-1246 expression was an independent prognostic factor of poor patient survival ($p= 0.036$; HR=2.82; 95% CI=1.07–7.43).

**Conclusions:** High miR-1246 expression is associated with poor prognosis in OSCC and may serve as a novel prognostic marker in OSCC.

**MeSH Keywords:** MicroRNAs • Mouth Neoplasms • Prognosis

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## Background

Oral squamous cell carcinoma (OSCC) accounts for more than 90% of all oral cancers and is the sixth most common type of cancer in the world [1]. About 275 000 new cases of OSCC are diagnosed each year globally [2]. The 5-year survival rate of OSCC has not improved much over the past 2 decades [3]. In China, evidence has shown that the risk of morbidity for OSCC patients is still high and that OSCC tends to occur among younger patients [4]. Thus, much research effort is needed to address this public health threat worldwide.

The prognostic value of the traditional TNM system is widely regarded as inadequate in patients with OSCC [5]. Advances in understanding of the molecular mechanisms underlying OSCC have led to an ever-increasing number of molecular markers shown to be related to the behavior of this disease. However, little clear evidence has been provided on the prognostic relevance of these markers. In addition, there is an increased necessity for identification and standardization of sensitive and accurate biomarkers that can identify OSCC patients with a poor prognosis [6].

MicroRNAs (miRNAs) are small, noncoding RNAs found in eukaryotic cells. Mature miRNAs are small (20–21 nucleotides in length) endogenous noncoding RNAs that regulate the expression of over 50% of human genes at the post-transcriptional level guided by partial complementarities to specific sequences in their target messenger RNA [7]. miRNAs is indispensable for a variety of basic biological and pathological processes, and miRNA signatures are closely correlated with human diseases. Deregulations of microRNA have been reported in various cancers, and have been showed to play important roles in cancer initiation and progression [8–11]. Distinct miRNA expression profiles in OSCC in comparison with matched healthy controls have been demonstrated, indicating miRNAs may participate in OSCC tumorigenesis [8,12]. Recently, various studies have shown that microRNA-1246 (miR-1246) plays a crucial role in regulation of cancer cell biological functions such as proliferation, invasion, and metastasis [13,14]. In addition, overexpression of miR-1246 has been found in several types of cancers such as liver cancer, pancreatic cancer, and colorectal carcinoma [13,15,16]. However, data on the expression of miR-1246 in OSCC and its clinical impact on patient survival remain scarce.

In the present study we aimed to evaluate the clinical significance of miR-1246 expression in OSCC. The expression level of the miR-1246 was examined in tumor and adjacent normal tissues. In addition, the relationship between miR-1246 expression and clinicopathological characters was analyzed and the impact of miR-1246 expression on the prognosis of OSCC patients was estimated.

## Material and Methods

### Patients and samples

This study was approved by the Research Ethics Committee of the Second Affiliated Hospital of Nanchang University. Written informed consent was obtained from all patients. The selection criteria for patients with OSCC were: (1) histological confirmation of OSCC and (2) no prior history of other cancers. All patients were diagnosed and treated at the Second Affiliated Hospital of Nanchang University from March 2009 to June 2014. Tumor stage was classified according to the 7$^{th}$ edition of the classification of malignant tumors of the American Joint Committee on Cancer [17]. Tumor grade was classified following the WHO (2005) criteria [18]. By last follow-up, 37 patients had died from the disease and the duration of follow-up was 60 months. Nine patients dropped-out from the study. The overall survival rate of OSCC patients in the study was 65.09%. For qRT-PCR, 106 pairs of fresh OSCC and matched adjacent normal tissue specimens were collected from patients who underwent surgery in the Second Affiliated Hospital of Nanchang University.

### Cell culture

The oral squamous cell carcinoma cell lines (SCC25 and CAL27) were maintained in Dulbecco's modified Eagle's medium (Gibco, Grand Island, NY, USA) containing 10% fetal calf serum (Gibco), 100 U/L penicillin, and 10 mg/L streptomycin. HOK16E6E7 cells, a human immortalized oral keratinocyte cell line, were cultured in keratinocyte growth medium containing 0.15 mM calcium and supplemented with epidermal growth factor (Gibco). All cells were cultured at 37°C in a humidified atmosphere with 5% $CO_2$.

### qRT-PCR

Total RNA was extracted from frozen tissues using TRIzol (Takara, Dalian, China) according to the manufacturer's instructions. Briefly, 2 ug of RNA was added to RT reaction, and the cDNA served as the template for amplification of PCR with sequence-specific primers (Sangon Biotech, Shanghai, China) using SYBR PrimeScript miRNA RT-PCR kit (Takara) in the Stratagene MX3000P real-time PCR system (Agilent Technologies, La Jolla, CA, USA). RNU6B gene was used as an internal control for normalization. The fold change between tumor tissues and noncancerous samples for miR-1246 was calculated with the $2^{-\Delta\Delta CT}$ method. The expression levels of miR-1246 in HOK16E6E7, SCC25, and CAL27 were detected using the same method. QRT-PCR was repeated in triplicate for each sample.

### Statistical analysis

The normality of data distribution was checked using the Shapiro-Wilk normality test (no significant differences from a





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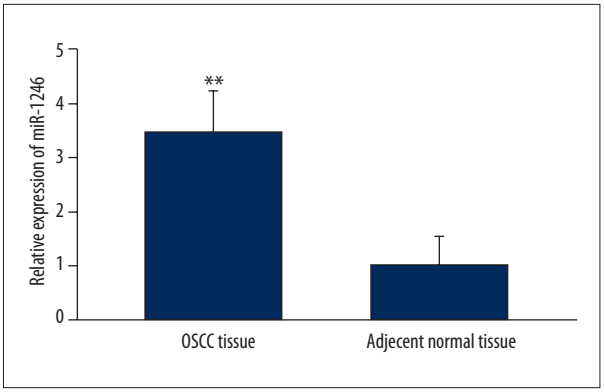


**Figure 1.** The expression level of miR-1246 in matched normal and tumor tissue samples.

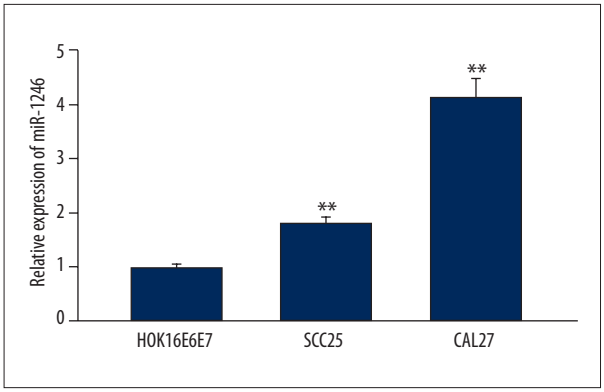


**Figure 2.** The expression level of miR-1246 in HOK16E6E7 cells, SCC25 cells and CAL27 cells.

normal distribution were detected; p=0.264). The comparison of the expression level of miR-1246 in tissues and cell lines was performed using two-sample Student's t-test. The correlation between the expression of miR-1246 and clinicopathological characters was assessed with chi-square test. The overall survival was analyzed by log-rank test, and survival curves were plotted. The univariate Cox regression was performed on each clinical covariate to examine its influence on patient survival.

Final multivariate models were based on stepwise addition. A Wald statistic of p<0.05 was used as the criterion for inclusion in final multivariate models. Multivariate analysis for prognostic factors was performed with Cox regression model. Statistical analysis was performed using SPSS version 21.0 software (Chicago, IL, USA) and Sigmaplot12.5 (Systat Software Inc., San Jose, CA, USA). The significance level was set at p<0.05

## Results

### Overexpression of miR-1246 in OSCC Tissues and cancer cell lines by qRT-PCR

We examined miR-1246 expression in 106 pairs of OSCC tissues and the neighboring healthy controls by qRT-PCR. MiR-1246 was expressed significantly higher in tumor tissues compared with corresponding noncancerous tissues (p<0.01; 3.47±0.78 *vs.* 1.00±0.54; Figure 1). Similarly, the miR-1246 expression level in OSCC cell lines CAL27 (p<0.01; 1.82±0.12 *vs.* 1.00±0.06; Figure 2) and SCC25 (p<0.01; 4.15±0.35 *vs.* 1.00±0.06; Figure 2) vastly increased compared to the control cell line.

### The Relationship between miR-1246 expression levels and clinicopathological features

The mean miR-1246 expression level of all OSCC was 3.47, which is utilized to divide OSCC patients into 2 groups. Forty-nine specimens were assigned to the high-expression group (equal to or higher than 3.47) and the remaining 57 specimens were assigned to the low-expression group (less than 3.47). The relationship between the relative miR-1246 expression levels and clinicopathological features of OSCC are shown in Table 1. There was no correlation between the relative miR-1246 expression levels and age, sex distribution, tumor location, tumor size, local recurrence, or distant organ metastasis (p>0.05), but the relative miR-1246 expression levels were significantly positively correlated with TNM stage (p=0.005), nodal status (p=0.015), and tumor grade (p=0.002).

### High-level expression of miR-1246 predicts poor prognosis in OSCC patients

Survival analysis was performed to evaluate whether miR-1246 expression levels could predict OSCC prognosis. Kaplan-Meier analysis showed that patients with higher levels of miR-1246 had significantly poorer survival than patients with lower miR-1246 expression levels (P=0.002; 55.11% *vs.* 81.71%; mean survival time 56.40±1.58 *vs.* 42.84±2.63; Figure 2).

A Cox proportional hazard regression model was developed to evaluate the association between the potential prognostic markers and overall survival at multivariate level. The variables, including miR-1246 expression, nodal status, TNM stage, tumor grade, and local recurrence, were selected in the final multivariate model because their Wald test p values were less than the generally used criterion of 0.05. The results revealed that miR-1246 expression (p=0.036; HR=2.82; 95% CI=1.07–7.43), TNM stage (p=0.003; HR=2.97; 95% CI=1.46–6.05) and tumor grade (p=0.006; HR=3.04; 95% CI=1.37–6.74) were independent prognostic parameters for OSCC (Table 2).

## Discussion

OSCC are cancers of the mucosal surfaces of the lips, floor of mouth, oral tongue, buccal mucosa, lower and upper gingiva,





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**Table 1.** A comparison of miR-1246 expression in OSCC and clinicopathological features.

| Variables | miR-1246 expression | | | | p value |
|---|---|---|---|---|---|
| | High expression n=49 | | Low expression n=57 | | |
| Age (years) | | | | | 0.642 |
| <60 | 21 | (19.81%) | 27 | (25.47%) | |
| ≥60 | 28 | (26.41%) | 30 | (28.30%) | |
| Sex distribution | | | | | 0.838 |
| Male | 30 | (28.30%) | 36 | (33.96%) | |
| Female | 19 | (17.92%) | 21 | (19.81%) | |
| Tumor location | | | | | 0.250 |
| Tongue | 18 | (16.98%) | 25 | (23.58%) | |
| Floor of mouth | 4 | (3.77%) | 0 | (0.00%) | |
| Buccal mucosa | 12 | (11.32%) | 13 | (12.26%) | |
| Hard palate | 4 | (3.77%) | 4 | (3.77%) | |
| Upper or lower gingival | 11 | (10.37%) | 16 | (15.09%) | |
| Tumor size | | | | | 0.074 |
| T1–T2 | 30 | (28.30%) | 44 | (41.50%) | |
| T3–T4 | 19 | (17.92%) | 13 | (12.26%) | |
| Nodal status | | | | | 0.015 |
| N0–N1 | 29 | (27.36%) | 46 | (43.40%) | |
| N2–N3 | 20 | (18.87%) | 11 | (10.37%) | |
| TNM Stage | | | | | 0.005 |
| I–II | 25 | (23.58%) | 43 | (40.57%) | |
| III–IV | 24 | (22.64%) | 14 | (13.21%) | |
| Tumor grade | | | | | 0.002 |
| G1 | 13 | (12.26%) | 32 | (30.19%) | |
| G2/G3 | 36 | (33.96%) | 25 | (23.58%) | |
| Local recurrence | | | | | 0.191 |
| No | 23 | (21.70%) | 34 | (32.08%) | |
| Yes | 26 | (24.53%) | 23 | (21.70%) | |
| Distant organ metastasis | | | | | 0.379 |
| No | 41 | (38.68%) | 51 | (48.11%) | |
| Yes | 8 | (7.55%) | 6 | (5.66%) | |

hard palate, and retromolar trigone. It is becoming a serious and growing problem in many parts of the world because patients with OSCC often have disfigurement, loss of ability to eat and speak, and poor quality of life, especially in advanced cases [2]. Clinicopathological parameters such as tumor grade of differentiation and clinical stage have been used to evaluate the progression of OSCC but their sensitivity is relatively low. Therefore, finding novel effective biomarkers is of great significance for improving the outcome of OSCC therapy.

The expression levels of miRNAs are often changed in many cancers, resulting in abnormal increases or decreases [19–21]. These alterations play an important role in almost all facets of cancer development and progression [22]. Some miRNAs families have been shown to be involved in epithelial-to-mesenchymal





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**Table 2.** Multivariate analyses for prognostic factors in patients with OSCC.

| Variables | Hazard ratio (95% CI) | p value |
|---|---|---|
| Nodal status (N2–N3 *vs.* N1–N0) | 1.80 (0.75–4.32) | 0.191 |
| TNM Stage (III–IV *vs.* I–II) | 2.97 (1.46–6.05) | 0.003 |
| Tumor grade (G2/G3 *vs.* G1) | 3.04 (1.37–6.74) | 0.006 |
| Local recurrence (yes *vs.* no) | 1.75 (0.84–3.65) | 0.139 |
| MiR-1246 expression (high *vs.* low) | 2.82 (1.07–7.43) | 0.036 |

transition, which is an important component of cancer metastasis [23]. Thus, miRNAs are not only regarded as potential markers for cancer diagnosis, but also might serve as potential therapeutic targets by manipulating miRNA levels to enhance current cancer therapy outcomes.

Investigating the correlation between miRNA expression profiles and the prognosis of patients with OSCC may be beneficial to understanding the underlying molecular mechanisms involved in the cancer progression and enabling the identification of novel targets for OSCC treatment. In the present study, miR-1246 expression was shown to be correlated with advanced clinical stage, lymph node metastases, and histological grade, suggesting that miR-1246 might be involved in the carcinogenesis and metastasis of OSCC. In addition, we revealed that patients with a higher expression of miR-1246 tended to have much lower survival rates than patients with lower miR-1246 expression, indicating that high miR-1246 level is a potential biomarker for predicting the poor prognosis of OSCC.

Consistent with our study results, overexpression of miR-1246 has been observed in multiple tumor types, suggesting its important role in tumorigenesis. Della Vittoria Scarpati found that the expression level of miR-1246 is enhanced by about 2-fold in colorectal tumor tissue in comparison with stromal tissue [15]. There was no statistical difference between liver cancer and miR-1246 expression level, probably due to the small clinical sample of patients. However, the high expression of miR-1246 combined with low expression of cell adhesion molecule 1 (CADM1) was shown to be a risk factor for early-stage liver cancer [13]. A higher level of miR-1246 expression was correlated with a shorter survival time in patients with pancreatic cancer [16]. Piepoli et al. used miRNA expression profiles to find the difference between miRNA expressed in cancer tissues and that in normal tissues. MiR-1246 was shown to be significantly up-regulated by 12.01-fold and 9.37-fold in colorectal and pancreatic cancers compared to healthy controls, respectively [24]. Some studies have explored the exact molecular mechanism of miR-1246 in cancer development and progression. Cancer stem cells have been shown to be closely related with tumor initiation, progression, radioresistance, and chemotherapy resistance. Hasegawa found that miR-1246 could increase tumor-initiating potential and maintain cancer stem cell-like properties via CCNG2 in pancreatic cancer [16]. MiR-1246 has also been shown to specifically target the 3'-UTR of CADM1 and down-regulate its expression, which leads to enhancing migration and invasion capacity of hepatocellular carcinoma cell lines [13]. Enhanced miR-1246 expression can promote cervical cancer cell proliferation, invasion, and migration by suppression of its target gene, thrombospondin 2; suggesting that miR-1246 may be closely related with cervical cancer tumorigenesis and progression [14]. These studies indicate that miR-1246 might function as an oncogene and promote cancer progression. However, conflicting results about the expression level of miR-1246 were reported in esophageal squamous cell carcinoma (ESCC). Fu found that miR-1246 was increased in ESCC tissues, while another study showed that the expression level of miR-1246 was similar between ESCC tissues and normal controls [25,26]. Further large-scale investigations are needed to address conflicting findings on the expression level of miR-1246 in ESCC.

In addition to the overexpression of miR-1246 in various cancer tissues, miR-1246 is significantly enhanced in serum derived from nude mice implanted with primary human pancreatic ductal adenocarcinoma [27]. Moreover, serum miR-1246 has been showed to be up-regulated in patients with early-stage cervical squamous cell carcinoma, indicating that serum miR-1246 may be a promising biomarker for early detection of cervical squamous cell carcinoma [28]. Also, serum miR-1246 was significantly higher in primary colorectal cancer patients [29]. Similarly, circulating microRNA is increased in patients with ESCC and multiple myeloma [26,30].

Recent studies suggest that miR-1246 might also serve as a potential drug target or a biomarker to predict the risk of drug resistance and radioresistance. Hasegawa found that miR-1246 could increase induced drug resistance in pancreatic cancer *in vitro* [16]. Also, miR-1246 has been reported to be involved in





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promoting radioresistance of cervical cancer cells [31]. These findings suggest the possibility of a novel method to improve OSCC therapy by targeting miR-1246.

## Conclusions

In conclusion, the expression level of miR-1246 was increased in OSCC tissues and cell lines and it was correlated with TNM stage, nodal status, and tumor grade. In addition, high miR-1246 expression was associated with poorer survival and served as an independent prognostic factor in patients with OSCC, suggesting that miR-1246 may be a promising prognostic biomarker for OSCC. However, the relatively small sample of this study is a limitation; a larger sample size would definitely be desirable with longer follow-up to firmly establish the diagnostic value of miR-1246 in OSCC. In addition, further studies are needed to elucidate the role of miR-1246 in OSCC at the cellular level.

### Conflict of interest

We declare that we have no conflicts of interest.

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