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Non-coding RNA 886 Predicts HPV Status and Survival in Oropharyngeal Squamous Cell Carcinoma Patients

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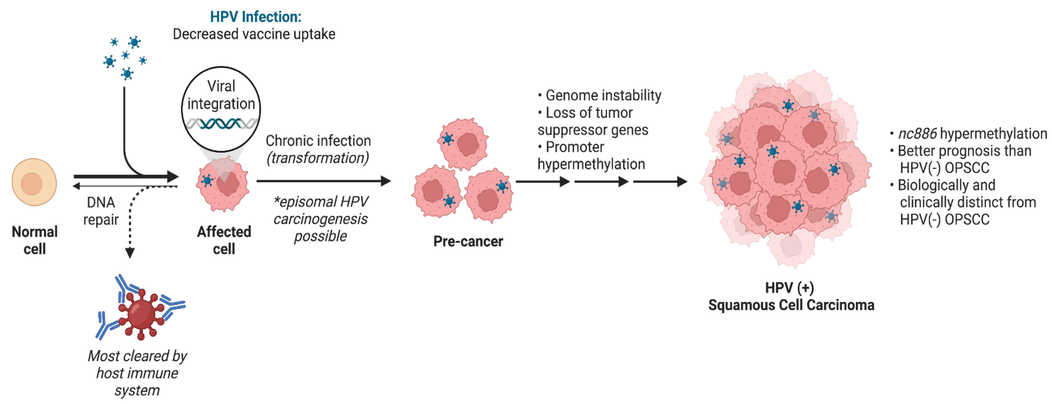
Introduction

Although the overall incidence of head and neck squamous cell carcinomas (HNSCC) has decreased over the past several years, the incidence of oropharyngeal squamous cell carcinoma (OPSCC), a subtype of HNSCC, has increased. Multiple studies show that this trend is due in part to rising HPV infections, as OPSCC has even surpassed cervical cancer as the most frequently diagnosed HPV-associated cancer.



This study investigates the serum expression levels of *nc886* in HPV(+) and HPV(-) OPSCC patients to elucidate the association of *nc886 expression* with HPV status and OPSCC survival.

Methods

- 83 newly diagnosed, histopathologically confirmed OPSCC patients recruited from the University of Texas MD Anderson Cancer Center (MDACC).
- Patients completed an epidemiological questionnaire asking about demographics and risk factors; clinical and follow-up data were abstracted from the electronic medical record.
- HPV16 status was determined by in-situ hybridization or specific RT-PCR in addition to a p16 immunohistochemical analysis as a standard clinical practice at MDACC.
- RT-qPCR for *nc886* was performed on patients who met inclusion criteria.

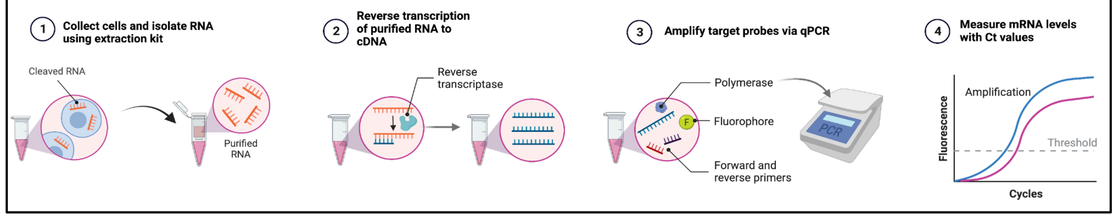


Table 1. Selected characteristics of 83 OPSCC patients

Variable	Number (%)	Variable	Number (%)
Age, years		**Alcohol use, mean number of drinks/week**	
≤ 57	51 (61.6)	≤15	48 (58.6)
> 57	32 (38.4)	>15	35 (41.4)
Sex		**Comorbidity**	
Male	69 (83.7)	None to mild	75 (90.5)
Female	14 (16.3)	Moderate to severe	8 (9.5)
Ethnicity			
White	72 (86.9)	**Overall stage**	
Other	11 (13.1)	I-II	6 (7.1)
Smoking		III-IV	77 (92.9)
Never	36 (43.1)	**HPV status**	
Current or Previous	47 (56.9)	(+)	63 (75.0)
Alcohol		(-)	20 (25.0)
Never	26 (31.4)	**Treatment**	
Current or Previous	57 (68.6)	X	23 (27.6)
Pack years of smoking		XC	60 (72.4)
≤ 10	49 (58.8)		
> 10	34 (41.2)		

X: Radiation (at 2 Gy/day for 33-35 days); C: Chemotherapy

Results

Fig 1. Serum nc886 expression and overall survival of all 83 OPSCC patients

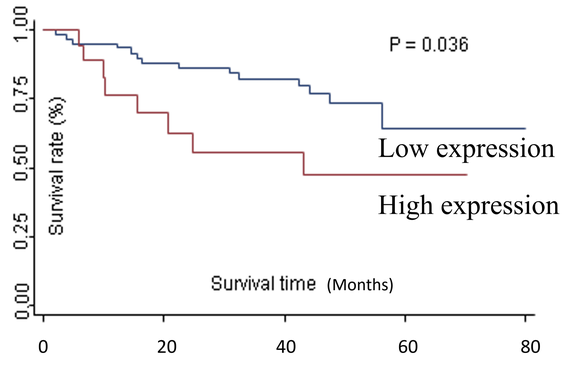


Fig 2. Serum nc886 expression and overall survival of 63 HPV(+) OPSCC patients

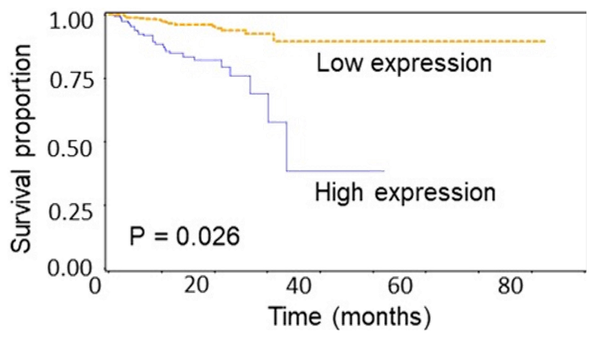


Table 2. Differences of serum nc886 expressions between HPV16(+) and HPV16(-) OPSCC patients

ncRNA	HPV16(+) (N = 63)		HPV16(-) (N = 20)		P-value
	Mean	**SD**	**Mean**	**SD**	
nc886	2.52	1.33	3.21	2.12	0.008

Analyses performed:

- Kaplan-Meier survival analysis on serum *nc886* expression levels in all OPSCC patients and HPV(+) OPSCC patients. (Figures 1 and 2).
- Comparison of serum *nc886* expression level between HPV(+) and HPV(-) OPSCC using an Independent Samples T-test (Table 2).
- Cox Proportional-Hazards Model to determine hazard ratio of Low *nc886* expression in HPV(+) OPSCC patients (Table 3).

Table 3. Low serum nc886 expression is associated with reduced risk of death in 63 HPV(+) OPSCC patients

nc886 expression	Total	Overall Death	HR* (95% CI)
High (> mean)	31	13	Reference
Low (≤ mean)	32	2	0.09 (0.01-0.56)

*Adjusted for age, sex, race, smoking/alcohol status, pack-years of smoking, stage, treatment, and comorbidity.

Discussion

Key Findings:

- Low expression of nc886 in serum is significantly associated with HPV(+) OPSCC tumors (p=0.008).
- Low expression of nc886 predicts better overall survival among OPSCC patients (p=0.036), particularly in HPV(+) OPSCC patients (p=0.026).
- Within HPV(+) OPSCC patients, those with low expression were 91% less likely (95% CI: 44-99%) to experience death than to those with high expression.

Interpretation:

- *Nc886* may play a different role in development and treatment response in HPV(+) and HPV(-) OPSCC.
- *Nc886* may involve in different molecular pathways, such as immunity, inflammation, and apoptosis, in HPV(+) and HPV(-) OPSCC patients, leading to different sensitivity to radiation or radio-chemotherapy.
- *Nc886* could be a future prognostic predictor and therapeutic target in HPV(+) OPSCC, while a larger, well-designed prospective study is needed for validation and *in vitro* and *in vivo* studies are required to explore the molecular mechanism underlying the association.

Limitations:

- The generalizability of this study is limited to MDACC patients only.
- Given the nature of hospital-based study, these findings could be biased due to several confounders.
- Additionally, these findings could be by chance due to a small cohort in this study, and a larger study is needed for replication and validation.

Future studies:

- Conducting larger prospective independent validation studies to verify our findings in other patient populations to increase generalizability.
- Further functional/mechanistic studies on roles of *nc886* in the etiology/prognosis of HPV-driven OPSCC.
- Developing a multi-ncRNA signature to predict prognosis of patients with OPSCC.

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