

Expression of ANCR in nasopharyngeal carcinoma patients and its clinical significance

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Abstract

Anti-differentiation non-coding RNA (ANCR), a long non-coding RNA, is involved in the development, progression and metastasis of various human cancers. However, its clinical significance in nasopharyngeal carcinoma (NPC) still remains unknown. This study aimed to investigate ANCR expression and its clinical significance in NPC.

Totally, 96 NPC tissues and 24 non-cancerous nasopharyngeal mucosa tissues were used. The levels of ANCR were determined by qRT-PCR. Relationship of ANCR with patient clinical characteristics, disease-free survival and overall survival (OS) was evaluated.

ANCR expression was increased in NPC tissues compared to non-cancerous nasopharyngeal mucosae. ANCR expression was significantly related to lymph node metastasis, clinical stage, and tumor differentiation ($P < .05$). Kaplan-Meier survival analysis revealed that high level of ANCR expression was significantly associated with poor disease-free survival but not with OS in NPC patients. Univariate analysis showed a significant association between increased ANCR expression and adverse OS ($P < .05$), but multivariate analysis suggested that ANCR could not be used as an independent prognostic factor for NPC patients.

ANCR is involved in the development and progression of NPC, but whether it can be used as an effective therapeutic target for NPC needs further study.

Abbreviations: ANCR = Anti-differentiation non-coding RNA, CRT = chemoradiotherapy, CT = contrast-enhanced computed tomography, DFS = disease-free survival, HCC = hepatocellular carcinoma, NPC = nasopharyngeal carcinoma, OS = overall survival.

Keywords: anti-differentiation noncoding RNA, nasopharyngeal carcinoma, prognosis

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CG and XM contributed equally to this work.

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1. Introduction

Nasopharyngeal carcinoma (NPC), is prevalent in Southeast Asia, especially in southern China.^[1] Most NPC cases are undifferentiated or poorly differentiated (WHO grade II or III) squamous carcinoma,^[2] and usually primarily treated with radiotherapy.^[3] Although great technical improvements have been achieved in tumor treatment over the past few years such as concomitant chemoradiotherapy (CRT) and helical tomotherapy, there are still 20–30% of NPC patients who develop distant metastasis in 5 years after initial treatment,^[4] and the treatment outcome is very unpromising after metastasis.^[5] Clinical tumor node metastasis (TNM) staging system is widely used to predict the dissemination of NPC.^[2] However, patients at the same clinical stage and underwent similar therapies often get different prognoses.^[5] Several molecular biomarkers, such as p27,^[6] KIF2A,^[7] and PD-1,^[8] have been recently evaluated as candidate prognostic factors for NPC, but their applications in clinical practice are very limited. Therefore, it is urgent to identify novel potential prognostic factors of NPC.

Long non-coding RNAs (lncRNAs, >200 nucleotides), a group of endogenous non-coding nucleic acids, play important roles in various cellular events and mechanisms, including cancer-associated pathways.^[9,10] While aberrant lncRNAs expression such as MALAT1,^[11] HOTAIR^[12] and SNHG6^[13] can serve as useful biomarkers for cancer diagnosis and prognosis, no valuable prognostic lncRNAs in NPC have been detected.^[9] Anti-differentiation non-coding RNA (ANCR), a single 855-base pair lncRNA first identified to be involved in cell undifferentiation,^[14] exerts different functions in various types of malignancies.^[14–16] For instance, it has been documented that ANCR attenuated the invasion and metastasis of breast cancer by

degrading EZH2.^[17] ANCR can inhibit non-small cell lung cancer cell migration and invasion by inactivating TGF- β pathway.^[18] Additionally, Wen et al reported that ANCR promoted hepatocellular carcinoma (HCC) metastasis through upregulating HNRNPA1 expression.^[19] However, the relationship between ANCR and NPC has not been thoroughly revealed.

In this study, we aim to investigate ANCR expression and its clinical significance in NPC. First, we examined the ANCR levels in NPC specimens and non-cancerous nasopharyngeal mucosa tissues. We then analyzed the relationship between ANCR and clinicopathologic characteristics of NPC. In addition, disease-free survival (DFS) and overall survival (OS) analyses were performed to investigate the prognostic value of ANCR. Our results found that increased ANCR expression in NPC was significantly related to lymph node metastasis, clinical stage, tumor differentiation and poor survival. However, ANCR was not identified as an independent prognostic factor for NPC patients. Our findings may reveal the clinical value of ANCR in NPC.

2. Methods

2.1. Patients and tissue specimens

We retrospectively searched the patient database of the Department of Otolaryngology, Dantu District People's Hospital, Zhenjiang, Jiangsu Province, China, and identified NPC patients who were treated from January 2010 to December 2018. A total of 96 patients with biopsy-confirmed nonkeratinizing squamous cell carcinoma-undifferentiated type of NPC (World Health Organization types of II or III) were enrolled in this study. The exclusion criteria included: 1) patients who had received radiotherapy or CRT before biopsy; 2) patients complicated with other malignant diseases; 3) patients with distant metastases; 4) patients with karnofsky performance score < 70; 5) patients who were lost to follow-up during retrospective interview; (6) patients with unavailable medical records. Fresh specimens were collected during biopsy, which were immediately stored in liquid nitrogen overnight and then transferred to -80°C for storage until total RNA extraction. Additionally, 24 non-cancerous nasopharyngeal mucosa tissues were collected from individuals with chronic nasopharyngitis.

All patients were well informed and signed the written consent form. This study was approved and supervised by the Scientific and Ethical Committee of Dantu District People's hospital (2017032).

2.2. Treatment summary

All patients were treated as follows. The routine detailed physical examination included electronic optic nasopharyngoscopy, contrast-enhanced computed tomography (CT) or magnetic resonance imaging of the entire head and neck, chest radiography, abdominal ultrasonography, hematology and biochemistry profiles. The clinical stage was defined on the basis of the International Union Against Cancer.^[20] Histological subtypes were evaluated by two different pathologists and classified according to the 6th edition of the TNM Classification of the International Union Against Cancer. All 96 patients received radiotherapy or CRT after diagnosis.^[21,22]

2.3. RNA extraction, cDNA synthesis and qRT-PCR

Total RNA was isolated from frozen specimens using TRIzol reagent (Takara, Dalian, China). Purity of the isolated RNA was measured

by NanoDrop ND-1000 (NanoDrop Technologies/Thermo Scientific, Wilmington, DE), and RNA integrity was assessed by standard denaturing agarose gel electrophoresis. cDNAs were synthesized with PrimeScript Reverse Transcriptase (Takara, Dalian, China). qRT-PCR was performed using FastStart Universal SYBR Green Master (Takara, Dalian, China) on ABI PRISM 7900HT Sequence Detection system (ABI Applied Biosystems, Foster City, CA). The gene specific primers used were as follows: ANCR, 5'-GACATTCCTGAGTCGTCTTCGAACGGAC-3' (forward) and 5'-TAGTGCGATTTAGAGCTGTACAAGTTTC-3' (reverse); GAPDH, 5'-GGAGCGAGATCCCTCCAAAAT-3' (forward) and 5'-GGCTGTTGTCATACTTCTCATGG-3' (reverse). PCR was performed in a 10 μ L reaction volume and the PCR procedure was an initial denaturation at 95°C for 30 sec followed by 40 cycles of 95°C for 5 sec, 60°C for 30 sec. All qRT-PCR reactions were repeated in duplicates, and the ANCR level was calculated by the $2^{-\Delta\Delta CT}$ method with GAPDH as a reference.

2.4. Follow-up

Follow-up data were obtained by phone, letter and outpatient clinical database. All the patients were followed up from the date of diagnosis to death or the lasted census date. The patients were followed up every 3 months in the first 2 years, and every 6 months thereafter or until death. Follow-up examination included physical examination, electronic optic endoscopy, biopsy, chest X-ray, CT/ magnetic resonance imaging, bone scan, and abdominal sonography or PET-CT. The follow-up end points were assessed with DFS and OS. OS was defined as the time (months) from the date of first treatment to death from any reasons or last follow-up. DFS was defined as the time from the date of first treatment to the first of recurrence or death. Participants who were lost to follow-up were considered censored.

2.5. Statistical analysis

Data were analyzed with the statistical software SPSS 17.0 (SPSS Inc., USA) or GraphPad Prism 5.0 (GraphPad Software Inc.). Data were expressed as mean \pm standard deviation (SD). We quantified and classified the ANCR into low or high expression using a 50% cut-off level. Student *t* test was used to compare the ANCR expression levels in tumor vs non-cancerous mucosae. The differences between epidemiological/clinical variables and the ANCR levels were analyzed by the Pearson Chi-square test or continuous correction Chi-square test. The Kaplan-Meier method was used to test the DFS and OS of patients with high ANCR expression and the difference in survival was assessed with Log-rank test. The univariate and multivariate Cox analyses were used to explore the influences of different prognostic factors on DFS and OS. The statistical significance was $P < 0.05$, and all tests were two-sided.

3. Results

3.1. Patient clinicopathological characteristics

The clinicopathological characteristics of these patients are summarized in Table 1. There were 36 patients (37.5%) at advanced T-stage (T3 and T4) and 72 patients (75.0%) at late clinical stage (III and IV). No case of distant metastasis was found. Pathological studies confirmed 18 cases (18.8%) of differentiated non-keratinizing carcinoma (DNKC), i.e. WHO

Table 1
Patient clinicopathological information and demographic data (n = 96).

Variable	No. (%)
Age (yr)	
≤54.0	48 (50.0)
>54.0	48 (50.0)
Gender	
Female	29 (30.2)
Male	67 (69.8)
T category	
T1-T2	60 (62.5)
T3-T4	36 (37.5)
LN metastasis	
N0-N1	40 (41.7)
N2-N3	56 (58.3)
M category	
M0	96 (100.0)
M1	0 (0.0)
Clinical stage	
I-II	24 (25.0)
III-IV	72 (75.0)
Histologic differentiation	
DNKC	18 (18.8)
UNKC	78 (81.2)
Treatment	
RT	10 (10.4)
CRT	86 (89.6)
Death	
Yes	41 (42.7)
No	55 (57.3)

CRT = chemoradiotherapy, DNKC = differentiated non-keratinizing carcinoma, LN = lymph node, RT = radiotherapy, UNKC = undifferentiated non-keratinizing carcinoma.

type II, and 78 cases (81.2%) of undifferentiated non-keratinizing carcinoma (UNKC), i.e. WHO type III. Only radiotherapy was applied to stage I to IIa patients (10 cases, 10.4%), and platinum-based CRT was applied to stage Ib to IVa-b patients (86 cases, 89.6%).

The follow-up time varied from 24 to 100 months, with a mean of 80.16 months. By the time of the last follow-up, 25 patients (26.0%) developed loco-regional recurrences, 19 patients (19.8%) developed distant metastases, and 15 patients (15.6%) developed both. Among 41 deaths, 39 (95.1%) patients died of NPC with recurrences or metastases, and 2 (4.9%) died of cardiovascular diseases.

3.2. ANCR expression in carcinomas and non-cancerous mucosae

We quantitatively determined the expression levels of ANCR in NPC specimens and non-cancerous mucosal epithelial tissues by qRT-PCR. The results showed that the mean levels of ANCR were 1.541 ± 0.373 in NPC specimens and 0.964 ± 0.303 in non-tumor mucosae (Fig. 1). Therefore, ANCR expression in tumor samples was much higher than in non-cancerous mucosae ($P < .01$).

3.3. Association of ANCR expression with clinicopathological features

The high and low ANCR expression was classified according to a 50% cut-off level. The associations of ANCR expression with

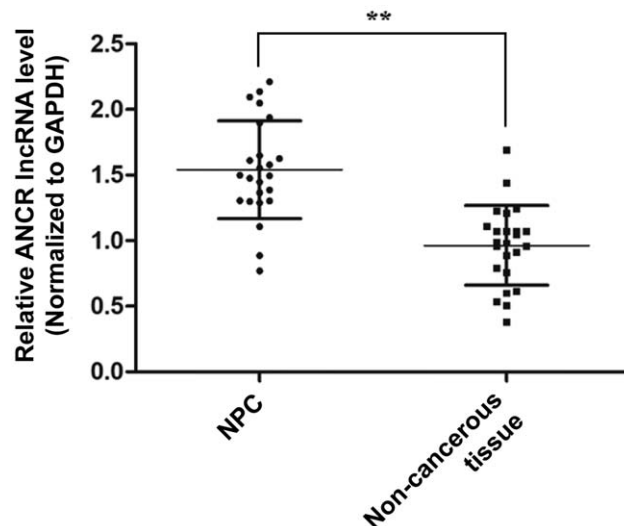


Figure 1. ANCR expression in NPC specimens and non-cancerous nasopharyngeal mucosa tissues detected by qRT-PCR. GAPDH was used as an internal control. Scatter plots were shown with mean \pm SD. ** $P < .01$.

clinicopathological features are showed in Table 2. The data revealed that the expression of ANCR was significantly related to the lymph node (LN) metastasis ($P < .05$), clinical stage ($P < .05$) and differentiation ($P < .05$). Other variables, including age, sex, and T stage, showed no statistically significant association with the expression of ANCR in NPC patients ($P > .05$).

3.4. Survival analysis and prognostic significance of ANCR expression

We then determined the prognostic value of ANCR expression in NPC patients. Kaplan-Meier analysis showed that the overall 5-

Table 2
Clinicopathologic variables associated with different expression patterns of ANCR.

Characteristics	No.	ANCR expression n (%)		P value
		Low	High	
Age (yr)				.221
≤54.0	48	21 (43.8)	27 (56.2)	
>54.0	48	27 (56.2)	21 (43.8)	
Sex				.505
Female	29	16 (55.2)	13 (44.8)	
Male	67	32 (47.8)	35 (52.2)	
T stage				.206
T1-T2	60	33 (55.0)	27 (45.0)	
T3-T4	36	15 (41.7)	21 (58.3)	
LN metastasis				.004*
N0-N1	40	27 (67.5)	13 (32.5)	
N2-N3	56	21 (37.5)	35 (62.5)	
Clinical stage				.005*
I-II	24	18 (75.0)	6 (25.0)	
III-IV	72	30 (41.7)	42 (58.3)	
Histologic differentiation				.036*
DNKC	18	13 (72.2)	5 (27.8)	
UNKC	78	35 (44.9)	43 (55.1)	

P values were determined by Pearson Chi-square tests. DNKC = differentiated non-keratinizing carcinoma, LN = lymph node, UNKC = undifferentiated non-keratinizing carcinoma. The high and low ANCR expression was classified according to a 50% cut-off level.

* $P < .05$.

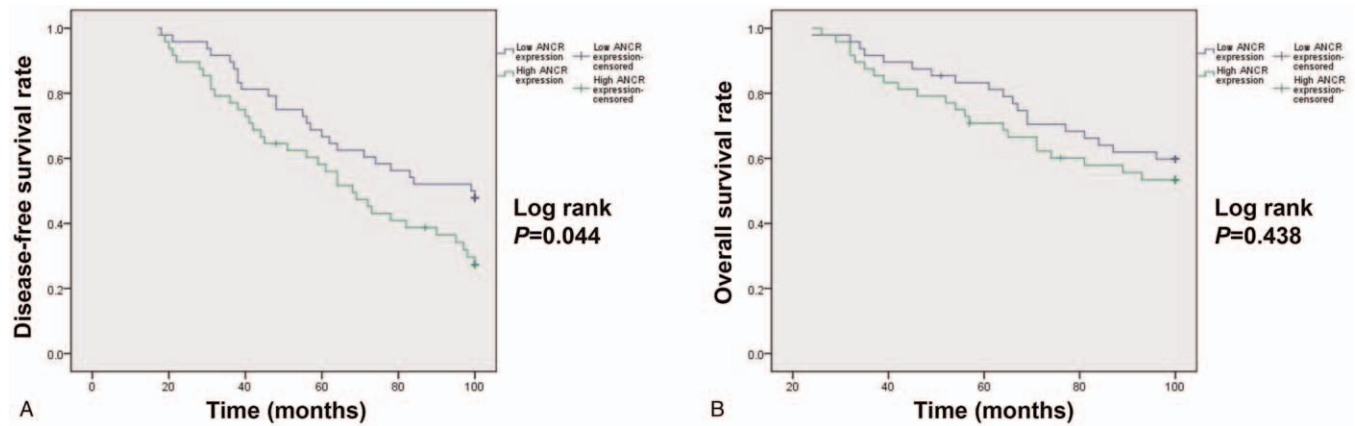


Figure 2. Survival analysis of NPC patients ($n=96$). Kaplan-Meier method was used for survival analysis and the difference in survival was assessed with Log-rank test. The expression of ANCR was classified into low or high expression using a 50% cut-off level. (A) Patients with high level of ANCR expression (green line) showed a significantly lower DFS rate. (B) Patients with high level of ANCR expression (green line) did not show a worse OS rate.

year DFS and OS rates were 62.4% and 77.0%, respectively. The 5-year DFS rate was 66.7% in the low ANCR expression group, and 58.1% in the high ANCR expression group. The 5-year OS rate was 83.3% in the low ANCR expression group, and 70.8% in the high ANCR expression group. The log-rank test indicated that NPC patients with low level of ANCR expression had significantly higher DFS rates ($P=.044$, Fig. 2A). However, there was no significant difference in OS between patients with low and high ANCR expression level ($P=.438$, Fig. 2B).

Furthermore, in the univariate analysis, we found that T stage (Hazard ratio [HR]=2.006, 95% confidence interval [CI]: 1.087–3.703; $P=.026$), LN metastasis (HR=2.106, 95% CI: 1.074–4.133; $P=.030$) and clinical stage (HR=3.008, 95% CI: 1.179–7.675; $P=.021$) were significantly related with OS; and that LN metastasis (HR=1.922, 95% CI: 1.119–3.304; $P=.018$), clinical stage (HR=2.204, 95% CI: 1.049–3.904; $P=.035$), and ANCR expression (HR=1.690, 95% CI: 1.007–2.836; $P=.047$) were significantly associated with DFS (Table 3). Additionally, the multivariate Cox regression analysis showed that T stage (HR=2.084, 95% CI: 1.128–3.848; $P=.019$) and LN metastasis (HR=2.186, 95% CI: 1.113–

4.292; $P=.023$) were independent prognostic factors for OS; and that LN metastasis (HR=1.922, 95% CI: 1.119–3.304; $P=.018$) was independent prognostic factor for DFS (Table 3).

4. Discussion/conclusion

NPC is different from non-nasopharyngeal head and neck carcinomas in several ways, including its pathological differentiation and strong sensitivity for radiotherapy.^[3] Previous studies have demonstrated that ANCR is a key regulator of keratinocyte differentiation where its expression is necessary to maintain the undifferentiated cell state.^[14,23] ANCR has also been reported being impaired in several cancers, such as colorectal cancer,^[24] lung cancer,^[18] and breast cancer.^[17] Because the main pathological features of NPC are poor differentiation or undifferentiation,^[1] we speculate that ANCR might play an important role in the development and progression of NPC.

Using qRT-PCR, we found that ANCR expression was much higher in NPCs than in non-cancerous mucosae. Moreover, ANCR expression had significant association with LN metastasis, clinical stage and histologic differentiation in NPC patients.

Table 3
Results of univariate and multivariate Cox regression analyses in 96 patients.

Parameter	Overall Survival		Disease-free Survival	
	HR (95% CI)	P value	HR (95% CI)	P value
Univariate analyses				
Age (≤ 54 vs >54)	0.871 (0.472–1.610)	.660	1.168 (0.701–1.947)	.551
Gender (Female vs male)	1.166 (0.604–2.251)	.648	1.120 (0.643–1.950)	.689
T stage (T1-T2 vs T3-T4)	2.006 (1.087–3.703)	.026*	1.421 (0.847–2.382)	.183
LN metastasis (N0-N1 vs N2-N3)	2.106 (1.074–4.133)	.030*	1.922 (1.119–3.304)	.018*
Clinical stage (I-II vs III-IV)	3.008 (1.179–7.675)	.021*	2.024 (1.049–3.904)	.035*
Differentiation (DNKC vs UNKC)	0.514 (0.262–1.008)	.053	0.729 (0.393–1.351)	.316
ANCR expression (Low vs high)	1.274 (0.689–2.353)	.440	1.690 (1.007–2.836)	.047*
Multivariate analyses				
T stage (T1-T2 vs. T3-T4)	2.084 (1.128–3.848)	.019*		
LN metastasis (N0-N1 vs N2-N3)	2.186 (1.113–4.292)	.023*	1.922 (1.119–3.304)	.018*
Clinical stage (I-II vs III-IV)	1.229 (0.315–4.788)	.766	1.366 (0.563–3.313)	.490
ANCR expression (Low vs high)			1.437 (0.840–2.459)	.186

CI=confidence interval, HR=hazard ratio, LN=lymph node.

* $P < .05$.

Therefore, the increased expression of ANCR may be involved in the invasive behaviors of NPC, as well as metastasis processes of NPC. These findings are consistent with previous findings of ANCR expression in HCC tissues.^[19] However, Li et al. reported that ANCR level was lower in breast cancer tissues in contrast to their normal counterparts.^[17] It may imply that the status and role of ANCR expression may vary across tumor types, and further researches are required. Our study also demonstrated that NPC patients with higher level of ANCR had significantly lower DFS rates after therapy. The ANCR expression was related with DFS in the univariate analysis, but it was not an independent prognostic indicator for NPC.

Metastasis is one of the unique clinical characteristics of NPC and the major obstacle for improving survival.^[25] Accumulative evidence suggests that epithelial mesenchymal transition (EMT) is strongly implicated in the progression and metastasis of NPC.^[26,27] It has also been reported that ANCR plays important roles in the modulation of EMT by EZH2,^[17] TGF- β ,^[18] and HNRNPA1.^[19] Studies have shown that increased ANCR expression can promote invasion and migration of colorectal cancer,^[24] and HCC.^[19] In contrast, Li et al demonstrated that silencing of ANCR promoted the metastasis in breast cancer.^[28] Wang et al showed that ANCR could inhibit non-small cell lung cancer cell migration and invasion.^[18] Therefore, ANCR-related tumor progression and metastasis may be specific to different cell and cancer types. Here, we noticed that ANCR might be an oncogene in NPC.

This study has some limitations. First, the sample size was relatively small. Secondly, we were unable to assess the ANCR expression levels in adjacent noncancerous mucosa because there was no matched noncancerous mucosa. Finally, due to the lack of EBV data in some NPC patients, the status of ANCR and its correlation with prognostic factor, EBV infection, couldn't be described in this study. Further studies with larger sample sizes are warranted.

5. Conclusion

Herein, we demonstrated that ANCR was up-regulated in NPC. Moreover, ANCR expression was associated with tumor differentiation, clinical stage, and cervical LN metastasis. ANCR expression negatively related with DFS rate after CT or CRT. However, it was not an independent prognostic indicator for NPC. These results suggest that ANCR is involved in the development and progression of NPC.

Author contributions

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