Original Article

ALDH1B1 predicts poor survival for locally advanced nasopharyngeal carcinoma patients

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Background: Distant metastasis and local recurrence remain the major reasons of treatment failure in locally advanced nasopharyngeal carcinoma (NPC). Therefore, exploring novel biomarkers for prognosis and sensitivity of radiotherapy in locally advanced NPC is crucial. This retrospective study evaluates the expression and prognostic value of aldehyde dehydrogenase 1B1 (ALDH1B1) for locally advanced NPC patients.

Methods: Sixty-seven locally advanced NPC patients and 22 chronic nasopharyngitis patients between September 2012 to November 2016 at The First Affiliated Hospital of University of South China were enrolled in this study. The expression of ALDH1B1 in tumor tissues were detected by using immunohistochemistry (IHC).

Results: Significant difference was observed between NPC groups and Pharyngitis tissues groups, and NPC groups has a higher ratio of high ALDH1B1 expression. ALDH1B1 expression were significantly associated with age and radiotherapy response. The Kaplan-Meier analysis indicated that patients with high ALDH1B1 expression had a poor prognosis both in overall survival (OS) and progression-free survival (PFS). Univariate analysis found that age, radiotherapy response and ALDH1B1 expression were correlated with OS. Besides, factors affecting PFS are radiotherapy response and ALDH1B1 expression. Multivariate analysis revealed that radiotherapy response and ALDH1B1 expression were the independent prognostic factors for OS, whereas radiotherapy response was for PFS.

Conclusions: The expression of ALDH1B1 was correlated with age and radiotherapy response. Patients with high ALDH1B1 expression show a poor prognosis both in OS and DFS. ALDH1B1 expression were the independent prognostic factors for OS.

Keywords: Aldehyde dehydrogenase 1B1 (ALDH1B1); nasopharyngeal carcinoma (NPC); prognosis; radioresistance

Submitted Sep 16, 2021. Accepted for publication Dec 26, 2021.
doi: 10.21037/tcr-21-1979
View this article at: https://dx.doi.org/10.21037/tcr-21-1979

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Introduction

In 2018, about 12,900 patients were diagnosed as nasopharyngeal carcinoma (NPC), which represent less than one percent of all new-onset cancers (1). However, its geographical global distribution is extremely unbalanced. Over 70% of new cases occur in south China and some regions of southeastern Asia. Despite the incidence and mortality had declined over the past decade, NPC still largely threaten local people's health (2). For the locally advanced NPC patients, current treatment strategies are radiotherapy and chemotherapy (induction, concurrent and adjuvant) (3). In addition, immunotherapy has achieved breakthroughs in anticancer treatment and has been considered as a promising future direction in the treatment of NPC (4). However, distant metastasis and local recurrence remain the major reasons of treatment failure in locally advanced NPC (5). Therefore, exploring novel biomarkers for prognosis and sensitivity of radiotherapy in locally advanced NPC is crucial.

Considerable evidences have supported that tumorigenesis and therapy resistance were associated with cancer stem cells (CSC) (6-8). The activity of CSC marker aldehyde dehydrogenase (ALDH), especially its isoform 1 (ALDH1), have been proven to be consistent with CSC activity in a variety of cancers. The ALDH1 plays a critical role in metabolizing and detoxifying the endogenous and exogenous aldehydes. The expression level of ALDH1 was also significantly associated with patients' prognosis in various cancers (9-11). Recent studies have indicated that ALDH1B1, a member of ALDH1 family, was overexpressed in various cancers. Meanwhile it plays an important role in tumorigenesis and therapy resistance (12-14). In addition, the high expression of ALDH1B1 was also associated with unfavored prognosis (15,16). However, the expression of ALDH1B1 and its prognostic role in NPC are still unclear.

In the present study, we have investigated the expression of ALDH1B1 and its prognostic role in locally advanced NPC. We found that ALDH1B1 was up-regulated in locally advanced NPC and associated with radiotherapy response. Patients with high ALDH1B1 expression had a poor survival. The results may provide novel prognostic marker and a potential therapeutic target for locally advanced NPC. We present the following article in accordance with the REMARK reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-1979/rc).

Methods

Patients

We retrospectively collected 67 locally advanced NPC patients and 22 chronic nasopharyngitis patients between September 2012 to November 2016 at The First Affiliated Hospital of University of South China. The eligibility criteria were as follows: (I) all patients with pathologically confirmed by pathology examination and the paraffin-embedded tissue samples were available for immunohistochemistry (IHC); (II) no history of other cancers; (III) no evidence of distant metastases; (IV) locally advanced disease (stage III or IVa) diagnosed by magnetic resonance imaging (MRI); (V) all patients received radical concurrent chemoradiotherapy in our hospital. We used the 8th American Joint Committee on Cancer (AJCC) staging system to classify the TNM stage of all the locally advanced NPC patients. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of The First Affiliated Hospital of University of South China (No. 2020110512007). The requirement for informed consent was waived.

Treatments

All patients had received external beam intensity-modulated radiation therapy (IMRT) concurrently combined with platinum-based chemotherapy. Radiotherapy was applied as follows: planned targeted volume (PTV)nx received 66–72 Gy, PTVnd received 64–70 Gy, PTV1 received 60–64 Gy, PTV2 received 50–54 Gy. The dosage of each PTV were delivered in 30 or 31 fractions over 6 weeks. During the period of radiotherapy, concurrent platinum-based chemotherapy (mainly DDP or DP) was also delivered every week. Besides, some patients (10 of 67) received two periods of induction chemotherapy.

We used response evaluation criteria in solid tumors (RECIST 1.1) to evaluate the efficacy of treatments (17). All patients were divided into radiosensitive and radioresistance groups according to the therapeutic effects after the completion of concurrent chemoradiotherapy. Radiosensitive patients were defined as patients with complete response or partial response over 12 months after the end of radical concurrent chemoradiotherapy. Radioresistance patients were defined as patients with progressive response or stable disease within 12 months after the end of radical concurrent

chemoradiotherapy (18,19).

IHC

IHC was performed according to the standard procedures. Briefly, all the paraffin-embedded specimen blocks were sliced into 4-μm-thick sections. Xylene was used to deparaffinize these sections and rehydrate them by alcohol gradient. Then, the paraffin sections were rinsed in 0.05% phosphate-buffered saline (PBS) and blocked with hydrogen peroxidase at room temperature for endogenous peroxidase ablation. Before IHC, heat retrieval with sodium citrate buffer and ethylenediaminetetraacetic acid (EDTA) repair were carried out. The samples were incubated with the anti-ALDH1B1 antibody (22220-1-AP, 1:300; Proteintech, China) overnight at 4 ℃ (16–18 h). After washing, the samples were incubated with the secondary antibody for 20 min, followed by color development with 3,3-diaminobenzidine (DAB) at room temperature in darkness for 3 min. The sections were counterstained with hematoxylin.

Two experienced pathologists who were blinded to the clinical data, independently evaluated the expression of ALDH1B1. The percentage of ALDH1B1 positive cells was graded as follow: 0=<5%, 1=5–24%, 2=25–49%, 3=50–74%, and 4=75–100%. The intensity of ALDH1B1 staining was graded as follow: 0= no staining, 1= low intensity, and 2= high intensity. The result was determined by the sum of these two scores, and this sum is referred to as the combined IHC staining score (CSS) (20). CSS was applied to divide the ALDH1B1 expression into two groups (low expression and high expression), low ALDH1B1 expression is from 0 to 3 while high ALDH1B1 expression is from 4 to 7.

Follow-up

After radical concurrent chemoradiotherapy, patients were followed-up every 3 months in the first year, every 6 months for the next 2 years, and finally at 1-year intervals until death. Radiologically examination was performed routinely during each follow-up visit. The primary endpoints of this study were overall survival (OS) and progression-free survival (PFS). The OS was defined as the time between the completion of radical concurrent chemoradiotherapy and death from any cause, the PFS was defined as the time between the completion of radical concurrent chemoradiotherapy and the date of progression or death.

Statistical analysis

Categorical variables were compared by χ^2 test or the Fisher's exact test. Kaplan-Meier curves were used to construct the survival curves and log-rank tests were used to analyze the difference. The Cox proportional hazards model was used for univariate and multivariate analysis. All the tests of significance were two-tailed: differences at P values <0.05 were considered significant. SPSS (version 22.0) was used to perform the statistical analyses.

The Cancer Genome Atlas (TCGA) data analysis

The Gene Expression Profiling Interactive Analysis (GEPIA), a user-friendly data portal, were used to analyze the mRNA expression of ALDH1B1 and its prognostic value in head and neck squamous cell carcinoma (HNSC) from the database of TCGA (21). GEPIA is available at http://gepia.cancer-pku.cn/.

Results

Patient characteristics

From September 2012 to November 2016, 67 pathologically confirmed locally advanced NPC patients (48 males and 19 females) who received radical concurrent chemoradiotherapy were enrolled in the study. The patients' characteristics are summarized in *Table 1*. The median follow-up time was 55.6 (range, 9.7 to 96.7) months. The median age was 50 (range, 24 to 74) years. Thirty patients (44.8%) had a smoking history. According to the World Health Organization (WHO), the histologic subtypes of NPC were classified as keratinizing squamous cell carcinoma (WHO type I), nonkeratinizing differentiated carcinoma (WHO type II), and nonkeratinizing undifferentiated carcinoma (WHO type III). Of all the patients, 26 patients were the WHO II and 41 patients were the WHO III. The clinical TNM stages III and IVa were 47 (70.1%) and 20 (29.9%), respectively. With respect to the radiotherapy response, the radiosensitive and radioresistance patients were 45 (67.2%) and 22 (32.8%), respectively.

Expression of ALDH1B1 in NPC

According to the results of IHC staining, ALDH1B1 protein was mainly located in cell cytosol (*Figure 1*). High ALDH1B1 expression was detected in 43.3% (29/67) NPC patients and 18.2% (4/22) chronic nasopharyngitis patients, which

Table 1 Patients' characteristics

Characteristics	N (%)
Age (years)	
≤50	34 (50.7)
>50	33 (49.3)
Sex	
Male	48 (71.6)
Female	19 (28.4)
Smoking	
Yes	30 (44.8)
No	37 (55.2)
WHO pathologic classification	
WHO II	26 (38.8)
WHO III	41 (61.2)
T stage	
T1–T2	29 (43.3)
T3–T4	38 (56.7)
N stage	
N0–N2	54 (80.6)
N3	13 (19.4)
TNM stage	
III	47 (70.1)
IVa	20 (29.9)
Radiotherapy	
Sensitive	45 (67.2)
Resistant	22 (32.8)
ALDH1B1 expression	
Low	38 (56.7)
High	29 (43.3)

WHO, World Health Organization; ALDH1B1, aldehyde dehydrogenase 1B1.

had significant difference (*Figure 2A*). We also investigate the expression of ALDH1B1 in HNSC from the database of TCGA. The results showed that ALDH1B1 was up-regulated in HNSC compared with normal tissue (*Figure 2B*).

The clinical characteristics between the high ALDH1B1 expression and low ALDH1B1 expression groups were also compared, and the results are listed in *Table 2*. ALDH1B1 expression was significantly correlated to age (P<0.001) and radiotherapy response (P=0.034). No significant differences were found in sex, history of smoking, pathological type, and TNM stage.

Prognostic value of ALDH1B1 expression

The 5-year PFS for low ALDH1B1 expression group and high ALDH1B1 expression group was 68.3% and 44.3%, respectively. The 5-year OS for low ALDH1B1 expression group and high ALDH1B1 expression group was 86.8% and 45.9%, respectively. The Kaplan-Meier survival curves showed that patients with high ALDH1B1 expression had an unfavorable prognosis both in PFS and OS (P=0.017 and P<0.001, respectively) (*Figure 3A*,*3B*). We also investigate the prognostic value of ALDH1B1 in HNSC from the date base of TCGA. The results indicated that no statistic difference was found between high and low ALDB1B1 expression group in DFS (*Figure 3C*). However, patients with high ALDH1B1 expression had a worse prognosis in OS (P=0.0034), which was in accordance with our results (*Figure 3D*).

To further investigate the prognostic value of ALDH1B1 expression, Cox proportional hazards model were performed to analyze the prognostic factors that affect the PFS and OS (*Tables 3*,*4*). The factors influencing patients' survival were evaluated by univariate analysis. As listed in *Table 3*, factors correlated with PFS are radiotherapy response (P<0.001) and ALDH1B1 expression (P=0.021). Our results showed that age (P=0.022), radiotherapy response (P=0.001) and ALDH1B1 expression (P=0.002) were significantly correlated with patients' OS (*Table 4*). The multivariate analysis, which consisted of all the positive prognostic factors in univariate analysis, revealed that radiotherapy response (P<0.001) was the independent prognostic factors for PFS, whereas radiotherapy response (P=0.004) and ALDH1B1 expression (P=0.036) were the independent prognostic factors for OS (*Tables 3*,*4*).

Discussion

NPC is the one of the most common malignancy in otolaryngology head and neck, and over 70% of new NPC occurred in south China and some regions of southeastern Asia (22). As NPC's location is difficult to detect and early symptoms is no obvious, NPC patients were usually diagnosed at an advanced stage. Radiotherapy are the primary therapeutic option for locally advanced

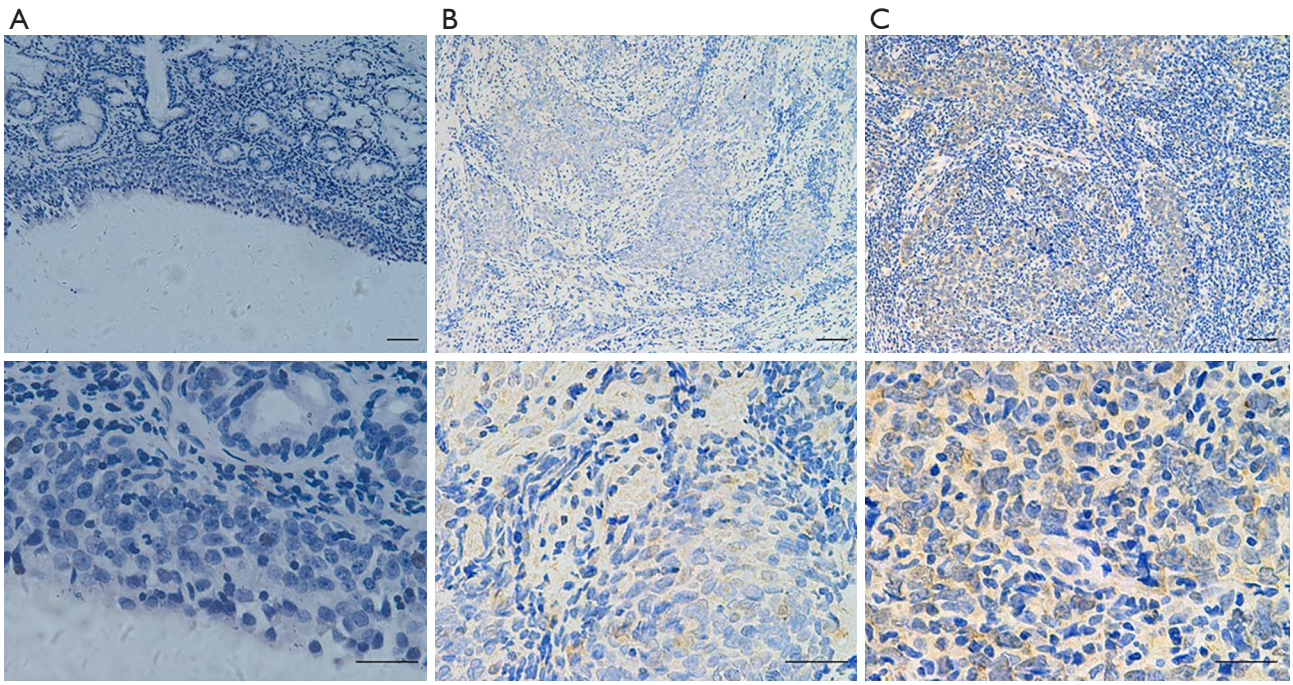

Figure 1 IHC staining of ALDH1B1 expressions in locally advanced NPC and chronic nasopharyngitis tissues (upper: magnification 100×, lower: magnification 400×). (A) ALDH1B1 expression in chronic nasopharyngitis tissues. (B) Low ALDH1B1 expression in locally advanced NPC tissues. (C) High ALDH1B1 expression in locally advanced NPC tissues. IHC, immunohistochemistry; ALDH1B1, aldehyde dehydrogenase 1B1; NPC, nasopharyngeal carcinoma.

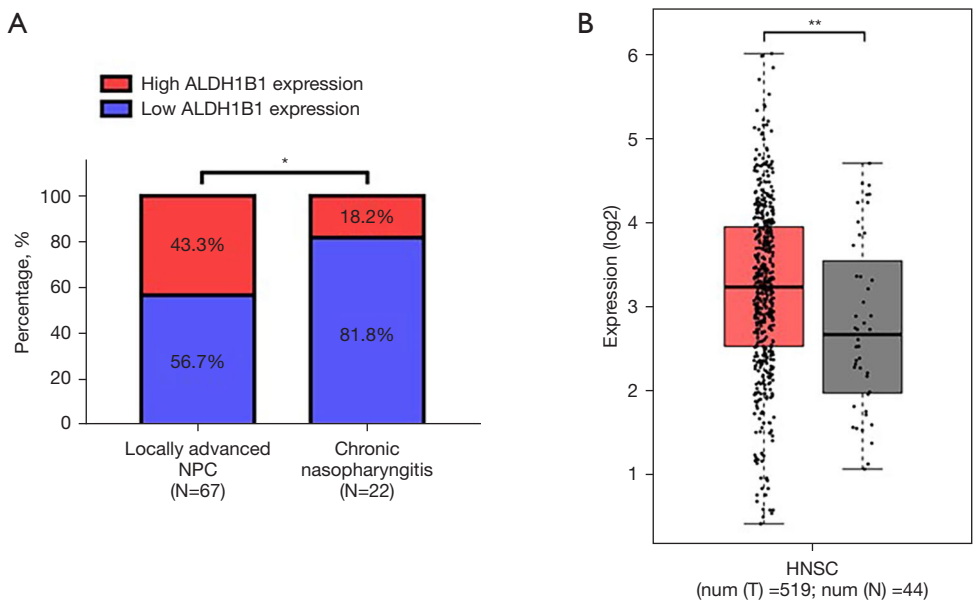

Figure 2 The expression level of ALDH1B1 in different tissues. (A) ALDH1B1 was significantly up-regulated in locally advanced NPC, compared with chronic nasopharyngitis tissues. (B) ALDH1B1 was significantly up-regulated in HNSC, compared with normal tissues. *P<0.05; **P<0.01. ALDH1B1, aldehyde dehydrogenase 1B1; NPC, nasopharyngeal carcinoma; HNSC, head and neck squamous cell carcinoma.

Table 2 Correlation between the clinicopathologic features and expression of ALDH1B1

Characteristics	N	ALDH1B1 expression, n (%)		χ^2	P
		Low	High		
Age (years)				14.484	<0.001
≤50	34	27 (79.4)	7 (20.6)		
>50	33	11 (33.3)	22 (66.7)		
Sex				0.448	0.590
Male	48	26 (54.2)	22 (45.8)		
Female	19	12 (63.2)	7 (36.8)		
Smoking				0.969	0.457
No	37	19 (51.4)	18 (48.6)		
Yes	30	19 (63.3)	11 (36.7)		
Pathological type				2.710	0.131
Undifferentiated	41	20 (48.8)	21 (51.2)		
Differentiated	26	18 (69.2)	8 (30.8)		
T stage				0.076	0.809
T1–T2	29	17 (58.6)	12 (41.4)		
T3–T4	38	21 (55.3)	17 (44.7)		
N stage				0.054	1.000
N0–N2	54	31 (57.4)	23 (42.6)		
N3	13	7 (53.8)	6 (46.2)		
TNM stage				0.034	1.000
III	47	27 (57.4)	20 (42.6)		
IVa	20	11 (55.0)	9 (45.0)		
Radiotherapy response				5.527	0.034
Sensitive	45	30 (66.7)	15 (33.3)		
Resistant	22	8 (36.4)	14 (63.6)		

ALDH1B1, aldehyde dehydrogenase 1B1.

NPC (3). Unfortunately, some NPC patients are resistant to radiotherapy, which leads to the treatment failure and increase the risk of distant metastasis or local recurrence (5). Therefore, it is of great significance to explore novel biomarkers to predict the prognosis and radiotherapy response of NPC patients. It also provides individual treatment strategy for the NPC patients who cannot benefit from radiotherapy.

The main reasons for the treatment failure of locally advanced NPC were resistance to radiotherapy, local recurrence, distant metastasis and avoidance of immunological surveillance (22). All these failures could be attributed to the CSC. CSC has strong self-renewal and differentiation potential. Moreover, it can regulate various cellular signaling pathways (such as Wnt/β-catenin, PI3K/AKT/mTOR, Hedgehog, etc.) to increase the local recurrence, distant metastasis and therapy resistance of tumor (23). ALDH, a marker in many CSC, played a critical role in drug and radiation resistance. Accumulating evidences have suggested that the failure of cancer treatment such as therapy resistance or disease progression could be contributed to the activity of ALDH (24-26).

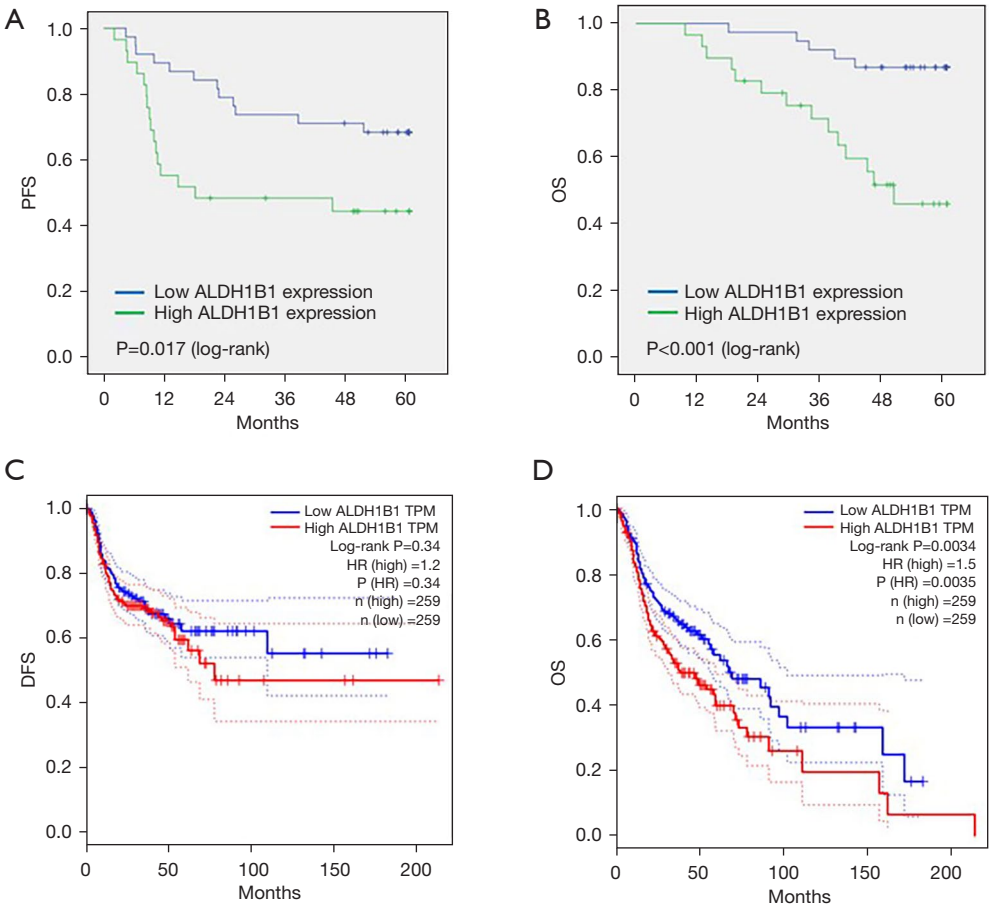

Figure 3 Correlation of ALDH1B1 and prognosis. (A,B) Locally advanced NPC patients with high ALDH1B1 expression had an unfavorable prognosis both in PFS and OS (P=0.017 and P<0.001, respectively). (C) No significant difference was found between ALDH1B1 expression and DFS in HNSC patients. (D) HNSC patients with high ALDH1B1 expression had a worse prognosis in OS (P=0.0034). ALDH1B1, aldehyde dehydrogenase 1B1; NPC, nasopharyngeal carcinoma; PFS, progression-free survival; OS, overall survival; DFS, disease-free survival; HNSC, head and neck squamous cell carcinoma.

Previous studies revealed that ALDH can eliminate the oxidative stress and increase the drug resistance (25). Some studies indicated that ALDH can enhance resistance to radiation through removing the free radicals generated by the radiolysis of water (26).

ALDH1B1 is a member of ALDH superfamily. Many studies have shown that ALDH1B1 was tightly associated with tumorigenesis and therapy resistance (12,13,27). It has been reported that up-regulating the expression of ALDH1B1 could enhance the resistance of colorectal cancer cells against doxorubicin, fluorouracil and etoposide (12). Singh *et al.* demonstrated that ALDH1B1 was highly expressed in human colonic adenocarcinomas and could promote colon cancer tumorigenesis by modulating the Wnt/β-catenin, Notch and PI3K/Akt signaling pathways (13). Wang *et al.* found that ALDH1B1 promote the tumorigenesis of osteosarcoma and was significantly correlated with poor prognosis in osteosarcoma patients (27). However, the expression of ALDH1B1 and its prognostic role in NPC are still unclear.

In this study, we reported the first study focusing on the impact of ALDH1B1 expression in prognosis and the association with clinical characteristics for locally advanced NPC. The expression level of ALDH1B1 in 67 locally advanced NPC and 22 chronic nasopharyngitis tissues were evaluated by IHC. Our results showed that ALDB1B1 was significantly up-regulated in NPC tissues compared with pharyngitis tissues, which indicated that ALDH1B1 may

Table 3 Cox regression for PFS analysis

Characteristics	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Age (years)	2.010	0.940–4.299	0.072			
Sex	2.033	0.773–5.350	0.151			
Smoking	0.753	0.353–1.609	0.464			
Pathological type	1.704	0.810–3.548	0.164			
T stage	1.513	0.697–3.285	0.295			
N stage	0.933	0.351–2.455	0.888			
TNM stage	2.027	0.947–4.337	0.069			
Radiotherapy response	18.467	7.580–44.993	<0.001	19.368	7.641–49.095	<0.001
ALDH1B1 expression	2.429	1.142–5.164	0.021	2.184	0.962–4.960	0.062

PFS, progression-free survival; ALDH1B1, aldehyde dehydrogenase 1B1.

Table 4 Cox regression for OS analysis

Characteristics	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Age (years)	3.296	1.185–9.163	0.022	1.151	0.503–4.781	0.445
Sex	2.483	0.723–8.528	0.149			
Smoking	0.859	0.345–2.138	0.744			
Pathological type	1.143	0.459–2.482	0.774			
T stage	1.365	0.536–3.472	0.514			
N stage	1.771	0.637–4.923	0.273			
TNM stage	2.223	0.892–5.541	0.086			
Radiotherapy response	5.300	2.072–13.558	0.001	4.073	1.569–10.570	0.004
ALDH1B1 expression	5.160	1.848–14.402	0.002	3.363	1.079–10.475	0.036

OS, overall survival; ALDH1B1, aldehyde dehydrogenase 1B1.

have the potential diagnostic value for NPC patients. The further analyses indicated that ALDH1B1 expression was significantly correlated to age and radiotherapy response. Elderly patients had a significantly high expression of ALDH1B1 compared with younger patients (66.7% *vs.* 20.6%, respectively). Consistent with what was expected before, patients with high ALDH1B1 expression are more likely to resistant to radiotherapy. Kaplan-Meier survival analysis revealed that patients with high ALDH1B1 expression had an unfavorable prognosis both in PFS and OS. In addition, ALDH1B1 expression were also the independent prognostic factors for OS in locally advanced NPC patients.

Notably, our research also showed some limitations. Since the study was a retrospective analysis of small sample size, larger sample size is needed to confirm the results. Only locally advanced NPC patients were enrolled in this study, other stage of NPC patients should be considered in future study. Furthermore, the present study did not investigate the function of ALDH1B1 *in vivo* and *in vitro* experiments, and the underlying mechanism of ALDH1B1 in tumorigenesis and radiation resistance should be

performed.

Conclusions

We have found that ALDH1B1 was correlated with radioresistance in locally advanced NPC patients. The high expression of ALDH1B1 predicted unfavorable survival both in OS and PFS. The results may provide a novel prognostic marker and a potential therapeutic target for locally advanced NPC.

Acknowledgments

We would like to thank Prof. Xiao-Ting Liu (PalmDrive Inc.) for her help in polishing our paper.
Funding: This study was supported by Hunan Province Natural Science Foundation (No. 2020JJ4543).

Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-1979/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-1979/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-1979/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of The First Affiliated Hospital of University of South China (No. 2020110512007). The requirement for informed consent was waived.

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Cite this article as: Zhu T, He JY, Liu YP, Deng K, Zuo JH, Ai XH. ALDH1B1 predicts poor survival for locally advanced nasopharyngeal carcinoma patients. Transl Cancer Res 2022;11(2):382-391. doi: 10.21037/tcr-21-1979

