ORIGINAL ARTICLE

Prognostic significance of AKR1B10 in patients with resected lung adenocarcinoma

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Abstract

Background: Aldo-keto reductases (AKRs) modify carbonyl groups on aldehyde or ketones to form primary or secondary alcohols, which are then conjugated with sulfates or glucuronide for excretion. The *AKR1B10* gene encodes a member of the AKR superfamily. Overexpression of AKR1B10 plays an important role in the tumorigenesis of lung cancer cells; however, the prognostic value of AKR1B10 expression in patients with lung adenocarcinoma has not been well demonstrated.

Methods: A total of 96 patients with resected lung adenocarcinoma were included in the study. AKR1B10 expression was determined by immunohistochemistry in tumor specimens. The prognostic value of AKR1B10 overexpression and its relationship with clinicopathological variables were investigated.

Results: AKR1B10 overexpression was identified in 22 (22.9%) of the 96 patients and tended to be significantly associated with N1 or N2 status ($P = 0.055$). AKR1B10 overexpression was not a significant prognostic factor for overall survival ($P = 0.301$) but was a significant prognostic factor for poor recurrence-free survival ($P = 0.015$). T status (T3 or T4 vs. T1 or T2; $P = 0.020$), N1 or N2 (vs. N0; $P = 0.019$), predominant pattern group (lepidic/acinar/papillary vs. micropapillary/solid; $P = 0.023$), and AKR1B10 overexpression ($P = 0.013$) were significant prognostic factors for poor recurrence-free survival in multivariate analysis.

Conclusions: AKR1B10 overexpression was a significant prognostic factor for poor recurrence-free survival in patients with resected lung adenocarcinoma. This information is useful to stratify patients at high-risk of recurrence after lung adenocarcinoma resection.

Introduction

Lung cancer is the main cause of cancer-related death worldwide.[1] Surgical resection is the treatment of choice for early-stage non-small cell lung cancer (NSCLC);[2] however, tumor recurrence after surgical resection is the most common cause of treatment failure.[3,4] Even with multimodality treatments, survival after recurrence is poor.[3,4] The identification of molecular markers predicting recurrence in lung adenocarcinoma patients after surgery will help to stratify high-risk patients for close follow-up or aggressive adjuvant therapy.

Aldo-keto reductases (AKRs) are monomeric soluble NAD(P)H-dependent oxidoreductases that catalyze the reduction of a variety of carbonyl groups.[5] AKRs can modify carbonyl groups on aldehyde or ketones to form primary or secondary alcohols, which are then conjugated with sulfates or glucuronide for excretion.[5] The human AKR1 subfamilies include the aldehyde reductases (AKR1A subfamily), aldose reductases (AKR1B subfamily), hydroxysteroid/dihydrodiol dehydrogenases (AKR1C subfamily), and steroid 5b-reductases (AKR1D subfamily).[6] The *AKR1B10* gene encodes a member of the AKR

superfamily.[6] Human *AKR1B10* is reported to be overexpressed in several human cancers, including lung and liver cancers.[7–11] *AKR1B10* is often overexpressed in male and smoking NSCLC patients, therefore *AKR1B10* has been proposed as a diagnostic marker in smokers with NSCLC.[7,8,12] The prognostic value of *AKR1B10* in human cancers has not been well investigated in the literature, and there are discrepancies over the prognostic value of *AKR1B10* in different human cancers. Liu *et al.* reported that increased *AKR1B10* is a prognostic factor for better overall survival (OS) and less metastasis in patients with hepatic cellular carcinoma (HCC).[9] Yoshitake *et al.* reported that *AKR1B10* is a predictor of recurrence after surgical treatment in cervical cancer.[13] Ludovini *et al.* reported that increased *AKR1B10* expression is associated with tumor recurrence in stage I lung adenocarcinoma.[14] *AKR1B10* overexpression plays an important role in the tumorigenesis of lung cancer cells;[15] however, the prognostic value of *AKR1B10* in lung cancer has not been well demonstrated.

Therefore, this study examines the prognostic significance of AKR1B10 expression and its relationship to clinicopathological variables in patients with resected lung adenocarcinoma.

Methods

The institutional review board of Taipei Veterans General Hospital approved this study. Patients who underwent anatomical resection for lung adenocarcinoma between January 2011 and December 2012 and had sufficient samples were included. Patients undergoing neoadjuvant treatment were excluded. A total of 96 patients were enrolled. Preoperative staging work-ups were routinely performed, as previously described.[16,17] Mediastinoscopy was only performed when a computed tomography scan showed enlarged mediastinal lymph nodes (diameter > 1.0 cm). The complete resection of lung cancer and mediastinal lymph node dissection/sampling was performed as previously described.[16,17] Determination of the disease stages was based on the seventh edition American Joint Committee on Cancer and International Union Against Cancer tumor node metastasis (TNM) classification.[18,19]

The indication for platinum-based adjuvant chemotherapy in our institution is pathologic stage II–IV disease after surgical resection. In our previous study, visceral pleural invasion and a micropapillary/solid–predominant pattern were significant predictors for recurrence in patients with resected stage I lung adenocarcinoma.[16] Although in the current study the use of adjuvant chemotherapy and the regimens used in patients with stage IB disease were not randomized but were administered according to physician preference, patients with a predominantly micropapillary/

solid pattern were more likely to be offered adjuvant chemotherapy.

All resected specimens were formalin fixed and stained with hematoxylin and eosin. After resection, follow-up of all patients was conducted quarterly at the outpatient department for the first two years, and semiannually thereafter. The modalities and protocols employed for follow-up were conducted as previously described.[16,17] The length of OS was defined as the interval between the date of surgical resection and the date of either death or the last follow-up. The length of recurrence-free survival (RFS) was defined as the interval between the date of surgical resection and the date of the first recurrence or last follow-up. An observation was censored at the last follow-up session when the patient was alive with recurrence-free status, or had died without recurrence.

Immunohistochemistry

The specimen processing and immunohistochemistry (IHC) procedures were performed as previously described.[20] A tissue microarray for IHC analysis was constructed from 6 mm diameter cores derived from lung adenocarcinoma specimens. The selected cores were representative of the whole tumor. The samples were fixed in formalin, air-dried, and then bathed in tris-buffered saline solution (pH 7.6). Endogenous peroxidase activity was blocked with 3% hydrogen peroxide for five minutes. To detect AKR1B10, a rabbit polyclonal antibody against AKR1B10 (catalogue number PA5-23017, Thermo Fisher Scientific, Waltham, MA, USA) was used at a dilution of 1:10 and incubated at room temperature for one hour. The detection was processed in the Discovery XT automated IHC/in situ hybridization slide staining system using the ultraView Universal DAB Detection Kit (Ventana Medical Systems, Inc. Tucson, AZ, USA), according to the manufacturer's instructions.

Immunohistochemical scoring

The immunoreactivity of AKR1B10 was graded from 0 to 2+ (0, no staining; 1+, weak staining; 2+, strong staining) according to the intensity of cytoplasmic expression. Only immunoreactivity of 2+ (strong staining) was considered a positive result of AKR1B10 overexpression.

Statistical analysis

The association between AKR1B10 expression and clinicopathological characteristics was analyzed using an $\chi 2$ test or a paired independent sample *t*-test, as appropriate. The log-rank test was used to make group comparisons. The OS and RFS were calculated using the Kaplan–Meier

Table 1 Clinicopathological variables in patients with resected lung adenocarcinoma

Variables	All patients
Age, years (mean ± SD)	64.7 ± 10.3
Gender, N (%)	
Male	42 (43.8)
Female	54 (56.2)
Smoking history, N (%)	
No	81 (84.4)
Yes	15 (15.6)
Smoking index, pack years (mean ± SD)	6.0 ± 18.8
T status, N (%)	
T1a	12 (12.5)
T1b	11 (11.5)
T2a	65 (67.7)
T2b	1 (1.0)
T3	6 (6.3)
T4	1 (1.0)
N status, N (%)	
N0	82 (85.4)
N1	3 (3.1)
N2	11 (11.5)
Pathologic stage, N (%)	
IA	21 (21.9)
IB	58 (60.4)
IIA	2 (2.1)
IIB	2 (2.1)
IIIA	13 (13.5)
Visceral pleural invasion, N (%)	
Absent	74 (77.1)
Present	22 (22.9)
Predominant pattern group, N (%)	
Lepidic/acinar/papillary predominant	84 (87.5)
Micropapillary/solid predominant	12 (12.5)
EGFR mutation, N (%)	
Absent	9 (9.4)
Present	32 (33.3)
Unknown	55 (57.3)
Adjuvant chemotherapy, N (%)	
No	37 (38.5)
Yes	59 (61.5)
AKR1B10 overexpression, N (%)	
No	74 (77.1)
Yes	22 (22.9)

SD, standard deviation.

method. Univariate and multivariate analyses were performed using the Cox proportional hazards model and SPSS version 20 (IBM Corp., Armonk, NY, USA). All

variables of $P < 0.1$ in univariate analysis were entered into multivariate analysis; however, for T and N status and TNM stage, only T and N status were entered. Statistical significance was defined as $P < 0.05$.

Results

Over a median follow-up duration of 29.9 months (range: 7.8–72.1), the five-year OS rate was 94.3%. The characteristics of the 96 lung adenocarcinoma patients are listed in Table 1. All patients underwent anatomical resection, including segmentectomy in 1 patient, lobectomy in 93, bilobectomy in 1, and pneumonectomy in 1. A total of 59 (61.5%) patients received adjuvant chemotherapy. Only three patients received adjuvant radiotherapy. During the follow-up period, 90 (93.8%) patients were alive, 5 (5.2%) had died, and survival status was unknown in 1 patient (1.0%). Tumor recurrence had developed in 23 (24.0%) patients.

AKR1B10 expression and its association with clinicopathological factors in lung adenocarcinoma

To determine AKR1B10 expression, 96 lung adenocarcinoma samples were subjected to immunohistochemical analysis. A representative case of immunohistochemical staining is shown in Figure 1. AKR1B10 expression was shown in 22 (22.9%) of the 96 lung tumor samples (Table 1). The relationship between AKR1B10 overexpression and clinicopathological variables is shown in Table 2. AKR1B10 overexpression tended to be significantly associated with N1 or N2 status ($P = 0.055$). No significant associations were identified between other clinicopathological variables and AKR1B10 overexpression. There was no significant association between AKR1B10 overexpression and smoking history ($P = 0.707$) or smoking index (pack-years) ($P = 0.587$). Seven of the 15 patients with a smoking history were current smokers.

We further examined whether there was a significant association between AKR1B10 overexpression and current smokers. The results showed that there was no significant association between AKR1B10 overexpression and current smokers ($P = 0.712$). There was no significant association between AKR1B10 overexpression and predominant
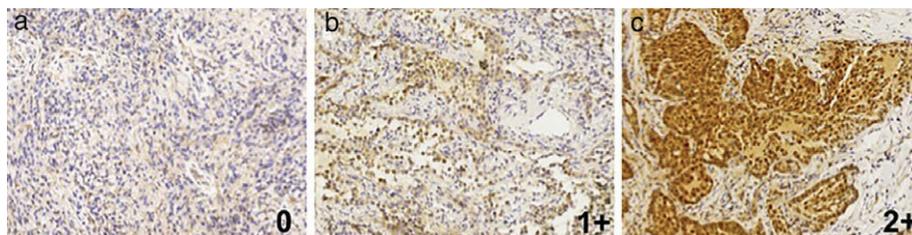

Figure 1 Representative immunohistochemical staining of *AKR1B10* in lung adenocarcinoma tumors scored (**a**) 0, (**b**) 1+, and (**c**) 2+ (original magnification, ×200).

Table 2 Relationship between *AKR1B10* overexpression and clinicopathological variables in patients with lung adenocarcinoma

Variables	AKR1B10 overexpression		P
	No (*n* = 74)	Yes (*n* = 22)	
Age, years (mean ± SD)	65.0 ± 10.5	63.8 ± 9.8	0.643
Gender, N (%)			
Male	29 (39.2)	13 (59.1)	0.099
Female	45 (60.8)	9 (40.9)	
Smoking history, N (%)			
No	63 (85.1)	18 (81.8)	0.707
Yes	11 (14.9)	4 (18.2)	
Smoking index, pack years (mean ± SD)	6.6 ± 20.8	4.1 ± 9.6	0.587
T status, N (%)			
T1 or T2	69 (93.2)	20 (90.9)	0.712
T3 or T4	5 (6.8)	2 (9.1)	
N status, N (%)			
N0	66 (89.2)	16 (72.7)	0.055
N1 or N2	8 (10.8)	6 (27.3)	
Pathologic stage, N (%)			
I	64 (86.5)	15 (68.2)	0.097
II	3 (4.1)	1 (4.5)	
III	7 (9.4)	6 (27.3)	
Visceral pleural invasion, N (%)			
Absent	22 (29.7)	9 (40.9)	0.325
Present	52 (70.3)	13 (59.1)	
Predominant pattern group, N (%)			
Lepidic/acinar/papillary predominant	66 (89.2)	18 (81.8)	0.359
Micropapillary/solid predominant	8 (10.8)	4 (18.2)	
EGFR mutation, N (%)†			
Absent	7 (24.1)	2 (16.7)	0.599
Present	22 (75.9)	10 (83.3)	

†Patients with unknown status were excluded from the analysis. SD, standard deviation.

pattern group (lepidic/acinar/papillary vs. micropapillary/solid; *P* = 0.359) or *EGFR* mutation status (*P* = 0.599).

Analysis of overall survival

Univariate analysis indicated that older age (hazard ratio [HR] 1.094, 95% confidence interval [CI] 1.003–1.195; *P* = 0.043) was a significant prognostic factor for poor OS (Table 3). AKR1B10 overexpression was not a significant prognostic factor of OS (*P* = 0.301) (Fig 2a, Table 3).

Analysis of recurrence-free survival

Univariate analysis indicated that T status (T3 or T4 vs. T1 or T2; HR 4.264, 95% CI 1.568–11.592; *P* = 0.004), N1 or N2 (vs. N0; HR 6.994, 95% CI 2.998–16.318; *P* < 0.001), pathologic stage (II or III vs. I; HR 7.154, 95% CI, 3.070–16.668; *P* < 0.001), and predominant pattern group (lepidic/acinar/papillary vs. micropapillary/solid; HR 4.593, 95% CI 1.866–11.307; *P* = 0.001) were significant prognostic factors for poor RFS (Table 3). AKR1B10 overexpression was also a significant prognostic factor for poor RFS

(HR 2.973, 95% CI 1.237–7.145; *P* = 0.015) (Fig 2b, Table 3). In multivariate analysis, T status (T3 or T4 vs. T1 or T2; HR 3.764, 95% CI 1.227–11.550; *P* = 0.020), N1 or N2 (vs. N0; HR 3.162, 95% CI 1.211–8.261; *P* = 0.019), predominant pattern group (lepidic/acinar/papillary vs. micropapillary/solid; HR 3.330, 95% CI 1.185–9.358; *P* = 0.023), and *AKR1B10* overexpression (HR 3.222, 95% CI 1.284–8.086; *P* = 0.013) were also significant factors for poor RFS Table 4.

Discussion

The results of this study demonstrate that *AKR1B10* overexpression is a significant prognostic factor for poor RFS in patients with resected lung adenocarcinoma. However, *AKR1B10* overexpression is not a significant prognostic factor for OS in patients with resected lung adenocarcinoma.

The associations between clinicopathological characteristics and *AKR1B10* expression in lung adenocarcinoma have not been well established. Because *AKR1B10* is often overexpressed in male and smoking NSCLC patients, *AKR1B10* has been proposed as a diagnostic marker in smokers with

Table 3 Univariate analysis of overall survival and recurrence-free survival in patients with resected lung adenocarcinoma

| Variables	HR	95% CI	*P*
Overall survival			
Age†	1.094	1.003 to 1.195	0.043
Female	1.172	0.196 to 7.022	0.862
Smoking history			
No	1		
Yes	0.038	0.000 to 1009.486	0.528
Smoking index, pack-years‡	0.926	0.719 to 1.194	0.555
T status			
T1 or T2	1		
T3 or T4	0.044	0.000 to 1 747 926	0.688
N1 or N2 (vs. N0)	4.511	0.753 to 27.009	0.099
Pathologic stage			
I	1		
II or III	3.405	0.569 to 20.391	0.180
Visceral pleural invasion	1.859	0.208 to 16.643	0.579
Predominant pattern group			
Lepidic/acinar/papillary predominant	1		
Micropapillary/solid predominant	5.351	0.891 to 32.143	0.067
Adjuvant chemotherapy	2.483	0.277 to 22.220	0.416
AKR1B10 overexpression	2.574	0.430 to 15.422	0.301
Recurrence-free survival			
Age†	1.023	0.983 to 1.065	0.259
Female	1.236	0.528 to 2.892	0.626
Smoking history			
No	1		
Yes	0.738	0.218 to 2.496	0.625
Smoking index, pack-years‡	0.997	0.973 to 1.022	0.825
T status			
T1 or T2	1		
T3 or T4	4.264	1.568 to 11.592	0.004
N1 or N2 (vs. N0)	6.994	2.998 to 16.318	<0.001
Pathologic stage			
I	1		
II or III	7.154	3.070 to 16.668	<0.001
Visceral pleural invasion	1.132	0.442 to 2.895	0.796
Predominant pattern group			
Lepidic/acinar/papillary predominant	1		
Micropapillary/solid predominant	4.593	1.866 to 11.307	0.001
Adjuvant chemotherapy	2.270	0.837 to 6.158	0.107
AKR1B10 overexpression	2.973	1.237 to 7.145	0.015

†An increase in the hazard ratio (HR) is associated with a one-year increase in age. ‡An increase in the HR is associated with one pack-year of additional smoking. CI, confidence interval.

NSCLC.[7,8,12] Wang *et al.* reported that smoking mediates the upregulation of *AKR1B10* expression in the airway epithelia of healthy smokers with no evidence of lung cancer, and proposed that the smoking-induced upregulation of *AKR1B10* may be an early process in the multiple events leading to lung cancer.[21] Our study showed that AKR1B10 overexpression tended to be significantly associated with N1 or N2 status (vs. N0). There was no significant association between AKR1B10 overexpression and smoking history (*P* = 0.707) or smoking index (pack-years) (*P* = 0.587). There was also no significant association between AKR1B10 overexpression and current smokers

(*P* = 0.712). However, only 15 (15.6%) of the 96 patients in our cohort had a smoking history and only seven of the 15 were current smokers. The number of patients with a smoking history in our study was small; thus, further study with a larger number of patients with a smoking history is needed to demonstrate the impact of smoking and AKR1B10 in lung adenocarcinoma.

The prognostic value of *AKR1B10* in human cancers remains controversial. Liu *et al.* reported that increased *AKR1B10* is a prognostic factor for better OS and less metastasis in patients with HCC.[9] Sonohara *et al.* reported that the ratio of *AKR1B10* messenger RNA levels in HCC

Figure 2 Kaplan–Meier survival curves for (**a**) overall survival and (**b**) recurrence-free survival stratified by *AKR1B10* over-expression (yes vs. no). (Log-rank test) (——) *AKR1B10* non-overexpression and (········) *AKR1B10* overexpression.
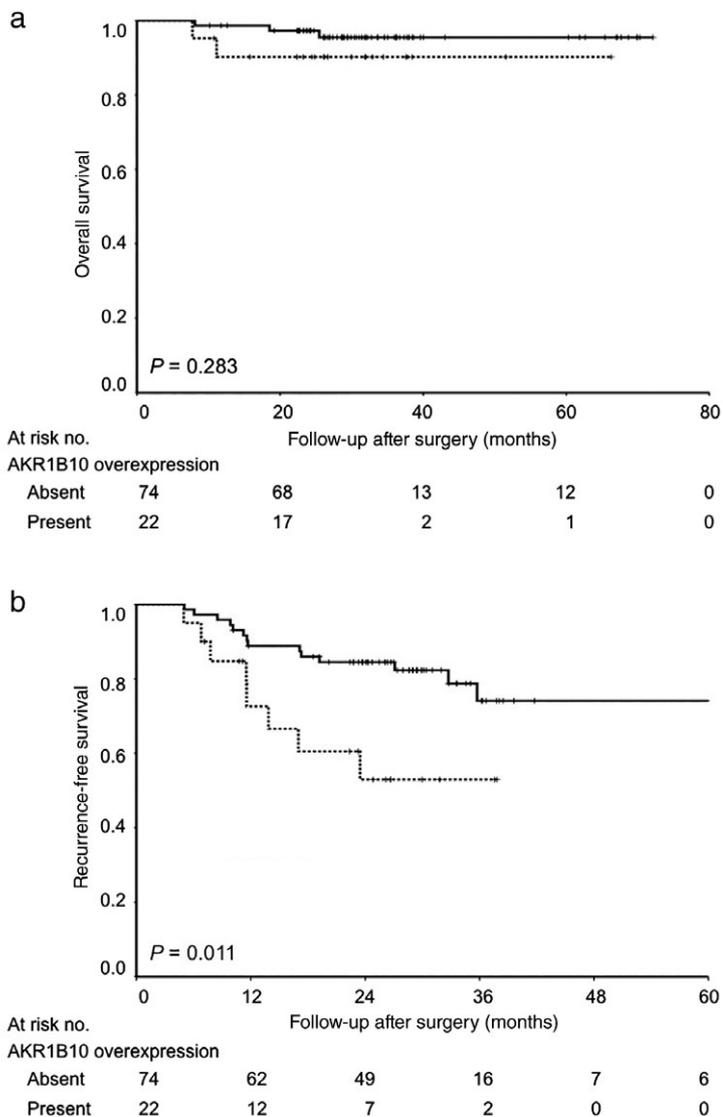
and corresponding non-tumorous tissues may predict prognosis after curative hepatectomy, with low expression in HCC tissue relative to non-tumorous tissue indicative of poor prognosis.[11] Yoshitake *et al.* reported that *AKR1B10* is a potential risk factor of recurrence after surgical therapy

in cervical cancer.[13] *AKR1B1* has been shown to be involved in many cellular processes relevant to cancer, such as epithelial-mesenchymal transition and angiogenesis.[22,23] The prognostic value and regulating mechanisms of *AKR1B10* in lung cancer have not been well demonstrated.

Table 4 Multivariate analysis of recurrence-free survival in patients with resected lung adenocarcinoma

Variables	HR	95% CI	P
T status			
T1 or T2	1		
T3 or T4	3.764	1.227 to 11.550	0.020
N1 or N2 (vs. N0)	3.162	1.211 to 8.261	0.019
Predominant pattern group			
Lepidic/acinar/papillary predominant	1		
Micropapillary/solid predominant	3.330	1.185 to 9.358	0.023
AKR1B10 overexpression	3.222	1.284 to 8.086	0.013

CI, confidence interval; HR, hazard ratio.

Zhou et al. showed that AKR1B10 expression is associated with cell proliferation, cell cycle, adhesion, and invasion, as well as with the extracellular-signal-regulated kinase/mitogen activated protein kinase signal pathway in lung adenocarcinoma cell lines.[15] They concluded that the overexpression of AKR1B10 in lung cancer plays an important role in the tumorigenesis of lung adenocarcinoma cells. Ludovini et al. reported that increased AKR1B10 expression is associated with tumor recurrence in stage I lung adenocarcinoma by microarray.[14] However, AKR1B10 was not related to survival in quantitative PCR validation in their study. Our study demonstrated the prognostic value of AKR1B10 in human lung adenocarcinoma specimens by IHC. The results showed that AKR1B10 overexpression was not a significant prognostic factor for OS; however, it was a significant prognostic factor for poor RFS in patients with resected lung adenocarcinoma. The OS of patients with resected stage I lung adenocarcinoma was good.[16] In our cohort, most of the patients (82.3%) had resected stage I lung adenocarcinoma. Furthermore, only 5 (5.2%) patients died during follow-up. Both of these factors may provide an explanation as to why AKR1B10 overexpression was not a significant prognostic factor for OS in our report.

There are some limitations and biases of this study. The patient cohort was relatively small and the follow-up period relatively short. Prospective multi-institutional studies are mandatory to further validate the prognostic value of AKR1B10 overexpression in patients with lung adenocarcinoma. Furthermore, the number of patients with a smoking history in the sample was small. Further evidence of the association between smoking exposure and AKR1B10 overexpression in patients with lung adenocarcinoma is required.

In conclusion, AKR1B10 overexpression is a significant prognostic factor for poor RFS in patients with resected lung adenocarcinoma. This information is helpful to identify patients at high risk of recurrence after resection of lung adenocarcinoma.

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Disclosure

No authors report any conflict of interest.

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