Pyruvate dehydrogenase E1α represents a reliable prognostic predictor for patients with non-small cell lung cancer resected via curative operation

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Background: Lung cancer is associated with a high morbidity and mortality rate worldwide; however, no reliable and independent prognostic predictor for non-small cell lung cancer (NSCLC) after curative surgery is available. Glucose metabolism is correlated with cancer cell proliferation. Pyruvate dehydrogenase E1α (PDH-E1α) catalyzes the conversion of pyruvate to acetyl-CoA and promotes aerobic glucose metabolism. In this study, we examined the relationship between PDH-E1α expression and clinicopathological factors associated with NSCLC to identify a reliable prognostic predictor of NSCLC after curative surgery.

Methods: A total of 445 patients with NSCLC who underwent curative resection were enrolled in this study. PDH-E1α expression was evaluated via immunohistochemistry. We analyzed the correlation between PDH-E1α expression and clinicopathological features of the patients.

Results: In total, 248 (56%) of the 445 patients with NSCLC were PDH-E1α-positive, and 197 patients were PDH-E1α-negative. PDH-E1α positivity was significantly correlated with the presence of adenocarcinoma (P<0.001) compared to the PDH-E1α-negative group. Patients with NSCLC showing PDH-E1α-negative expression had a significantly poorer overall survival rate (P=0.007) than those showing PDH-E1α-positive expression, especially at stage II. Patients with PDH-E1α negative expression also showed a poorer disease-free survival rate (P=0.02). Multivariate analysis revealed that PDH-E1α negativity (P=0.037) and male sex (P<0.001) were significantly correlated with a poor overall survival.

Conclusions: PDH-E1α may represent a reliable prognostic predictor for NSCLC in patients that have recently undergone curative resection, especially at stage II.

Keywords: Pyruvate dehydrogenase (PDH); non-small cell lung cancer (NSCLC); predictive marker; curative resection

Introduction

Lung cancer has a high morbidity and mortality rate worldwide, and is associated with the poor prognosis despite recent advances in therapy (1). Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers. Several clinicopathological prognostic factors, such as pathological stage, mutations in genes, and smoking history, have been reported to be associated with the outcome after surgery in patients with NSCLC (2,3); however, no reliable and independent prognostic predictor for NSCLC after curative surgery has been identified at present.

Glucose metabolism in cancer cells is increased considerably with increasing proliferation (4,5). In particular, anaerobic glycolysis is dominant even under aerobic conditions in the tumor microenvironment, which is known as the Warburg effect (6), suggesting that the enzymes involved in glucose metabolism in cancer cells may represent an important indicator of cancer malignancy (7,8). Among the glucose metabolism enzymes, the pyruvate dehydrogenase (PDH) complex catalyzes the conversion of pyruvate to acetyl-CoA and promotes aerobic glucose metabolism; PDH is phosphorylated by PDH kinase (PDK). The PDH-E1 enzyme, which is inhibited and regulated by the PDH complex, consists of a hetero-tetramer containing two α subunits and two β subunits. The E1-α subunit (PDH-E1α) contains the E1 active site and plays a key role in the function of the PDH complex (9). PDK activity has been reported in several types of carcinomas, such as colorectal cancer, bladder cancer, pancreatic cancer, and NSCLC (10-13). However, few studies have examined the relationship between PDH-E1α expression and clinicopathological factors associated with NSCLC. In this study, we aimed to determine whether PDH-E1α may serve as a prognostic predictor for NSCLC after curative surgery.

We present the following article in accordance with the REMARK reporting checklist (available at https://dx.doi.org/10.21037/jtd-21-1463).

Methods

Patient selection and ethical statement

We retrospectively investigated the clinical course of 665 patients with NSCLC who underwent surgery at Osaka City University, Osaka, Japan, between January 2010 and December 2016. Patients with R1 or R2 surgery, with preoperative chemotherapy or radiation therapy, and patients without curative resection, such as wedge resection, segmentectomy, and lobectomy without mediastinal lymph node dissection, were excluded. A total of 445 patients with histologically confirmed primary NSCLC with pathological stage 0 to stage IIIA who underwent R0 surgery (more than lobectomy and mediastinal lymph node dissection) were enrolled in this study. Pathological findings were determined according to 8th edition of the Union for International Cancer Control TNM classification. After final staging, the administration and regimen of adjuvant chemotherapy was appropriately determined by the cancer board consisting of a thoracic surgeon, a radiologist, and an oncologist. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Osaka City University Ethics Committee (Reference number 2019-006). Informed consent was obtained from all patients. All methods with respect to humans performed in accordance with the relevant guidelines and regulations.

Immunostaining of the PDH-E1α

In brief, paraffin-embedded sections from 445 patients were deparaffinized in xylene and hydrated in decreasing concentrations of ethyl alcohol. The sections were incubated with 3% hydrogen peroxide to block endogenous peroxidase activity. The sections were then heated for 10 min at 105 ℃ by autoclave in Target Retrieval Solution (DAKO, Carpinteria, CA, USA). Nonspecific binding was blocked via incubation with 10% normal rabbit serum for 10 min. The specimens were incubated with anti PDH-E1α antibody (sc-377092; 1:100; Santa Cruz Biotechnology, Dallas, TX, USA; RRID:AB_2716767) (14) at 4 ℃ overnight. These sections were incubated with a mouse linker for 10 min, and peroxidase-labeled polymer (Histofine SAB-PO(M) kit, Nichirei Biosciences Inc, Tokyo, Japan) for 5 min, followed by counterstaining with Mayer's hematoxylin.

Immunohistochemical determination

The immunoreactivity of PDH-E1α was evaluated according to the intensity of membranous staining at the deepest level of the tumor and the proportion of immunoreactive cells. Immunostaining intensity score was rated 0–3 as follows: 0, negative; 1+, weakly positive; 2+, positive; 3+, strongly positive (*Figure 1*). The immunostaining proportion score was measured as an estimate of the proportion of positive cells: 0, no
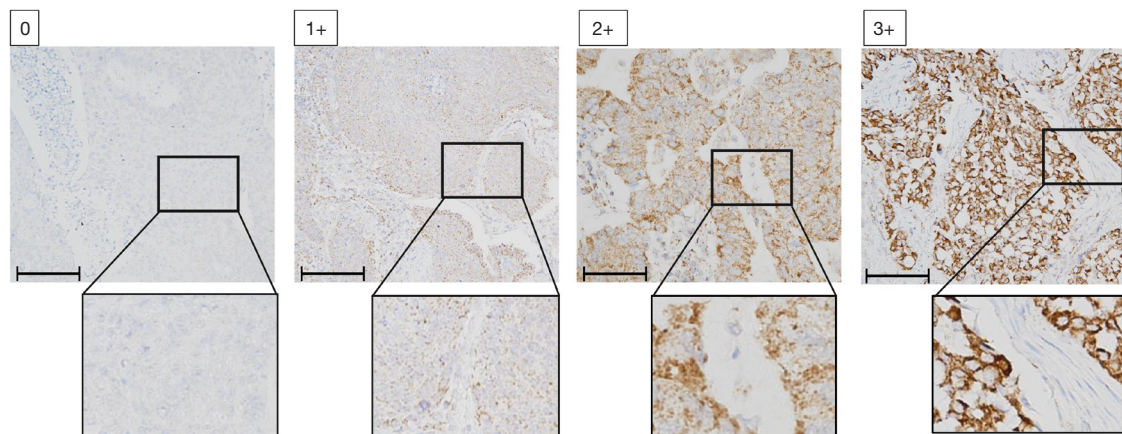
Figure 1 Representative images of immunostaining intensity of PDH-E1α expression in patients with NSCLC. Intensity score: 0, negative; 1+, weakly positive; 2+, positive; 3+, strongly positive. Bar, 50 µm. PDH-E1α, pyruvate dehydrogenase E1α; NSCLC, non-small cell lung carcinoma.

immunoreactive cells; 1+, <30% immunoreactive cells; 2+, 40–70% immunoreactive cells; 3+, >80% immunoreactive cells. The total score was calculated as the summation of the immunostaining intensity score and proportion score ranging from 0 to 6, and PDH-E1α expression was considered positive when the summation score was ≥4.

Statistical analysis

The χ^2 test was performed to determine the significance of differences between covariates. Survival durations were calculated using the Kaplan-Meier method and analyzed using the log-rank test to compare the cumulative survival durations in the patient groups. In addition, the Cox proportional hazards model was used to compute the multivariate hazard ratios for the study parameters. In all tests, a P value <0.05 was considered significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface of R, and more precisely, a modified version of the R commander (The R Foundation for Statistical Computing, Vienna, Austria) (15).

Results

Relationship between PDH-E1α expression and clinicopathological features

The clinicopathological features of all 445 patients based on PDH-E1α expression are summarized in *Table 1*. In

total, 248 patients (56%) of the 445 patients with NSCLC patients were PDH-E1α-positive and 197 patients were PDH-E1α-negative. PDH-E1α positivity was significantly correlated with the presence of adenocarcinoma (P<0.001) in comparison to the PDH-E1α-negative group. No other clinicopathological features were correlated with PDH-E1α expression, including induction of adjuvant chemotherapy and postoperative complications. There was no significant correlation between PDH-E1α expression and clinicopathological features in patients with adenocarcinoma or with squamous cell carcinoma, respectively.

Correlation between PDH-E1α expression and survival of patients with NSCLC

The 5-year overall survival rate according to PDH-E1α expression in all 445 patients is presented in *Figure 2*. Patients with NSCLC showing PDH-E1α-negative expression had significantly poorer survival rates (P=0.007) than those of patients showing PDH-E1α-positive expression. According to the pathological stages, the 5-year overall survival rate of patients with NSCLC showing PDH-E1α-negative expression was a significantly poorer (P=0.026) than those showing PDH-E1α-positive expression in stage II. In contrast, no significant difference was found between PDH-E1α expression in stages 0–I and III.

The 5-year disease-free survival rate, according to PDH-E1α expression in all 445 patients, is presented in *Figure 3*. Patients with NSCLC showing PDH-E1α-negative expression had significantly poorer survival

Table 1 Relationship between expression of PDH-E1α and clinicopathological features in 445 patients with NSCLC

Variables	Subgroup	PDH-E1α expression		
		Positive (n=248), n (%)	Negative (n=197), n (%)	P value
Age	<65	83 (33.5)	53 (26.9)	0.148
	≥65	165 (66.5)	144 (73.1)	
Sex	Female	95 (38.3)	60 (30.5)	0.089
	Male	153 (61.7)	137 (69.5)	
Smoking	Yes	178 (71.8)	135 (68.5)	0.466
	No	70 (28.2)	62 (31.5)	
Histology	Adenocarcinoma	185 (74.6)	114 (57.9)	<0.001
	Squamous cell carcinoma	50 (20.2)	70 (35.5)	
	Others	13 (5.2)	13 (6.6)	
Lymphatic invasion	Negative	168 (67.7)	137 (69.5)	0.758
	Positive	80 (32.3)	60 (30.5)	
Venous invasion	Negative	211 (85.1)	155 (78.7)	0.082
	Positive	37 (14.9)	42 (21.3)	
Pleural invasion	Negative	185 (74.6)	146 (74.1)	0.913
	Positive	63 (25.4)	51 (25.9)	
Depth of invasion	T1 or T2	218 (87.9)	166 (84.3)	0.271
	T3 or T4	30 (12.1)	31 (15.7)	
Lymph node metastasis	N0	199 (80.2)	147 (74.6)	0.169
	N1 or N2	49 (19.8)	50 (25.4)	
pStage	0–II	208 (83.9)	157 (79.7)	0.266
	III	40 (16.1)	40 (20.3)	

PDH-E1α, pyruvate dehydrogenase E1α; NSCLC, non-small cell lung carcinoma.

rates (P=0.02) than patients showing PDH-E1α-positive expression. According to the pathological stages, no significant difference was found between PDH-E1α expression in all stages.

There was no significant correlation between PDH-E1α expression and overall and disease-free survival rates in patients with adenocarcinoma or squamous cell carcinoma, respectively.

Univariate and multivariate analyses of survival

The results of the univariate and multivariate analyses of the overall survival are presented in *Table 2*. Univariate analysis showed that poor overall survival was significantly correlated with PDH-E1α negativity (P=0.007), male sex

(P<0.001), smoking (P=0.049), histology of adenocarcinoma (P=0.001), lymphatic invasion (P=0.006), pleural invasion (P=0.002), pathological T3/4 (P=0.02), and lymph node metastasis (P=0.014). Multivariate analysis revealed that PDH-E1α negativity (P=0.037) and male sex (P<0.001) were significantly correlated with poor overall survival.

Table 3 shows the univariate and multivariate analyses results of the disease-free survival. Univariate analysis showed that a poor disease-free survival was significantly correlated with PDH-E1α negativity (P=0.021), male sex (P<0.001), histology of adenocarcinoma (P=0.029), venous invasion (P<0.001), lymphatic invasion (P<0.001), pleural invasion (P<0.001), pathological T3/4 (P<0.001), lymph node metastasis (P<0.001), and adjuvant chemotherapy (P=0.005). Multivariate analysis revealed that male sex
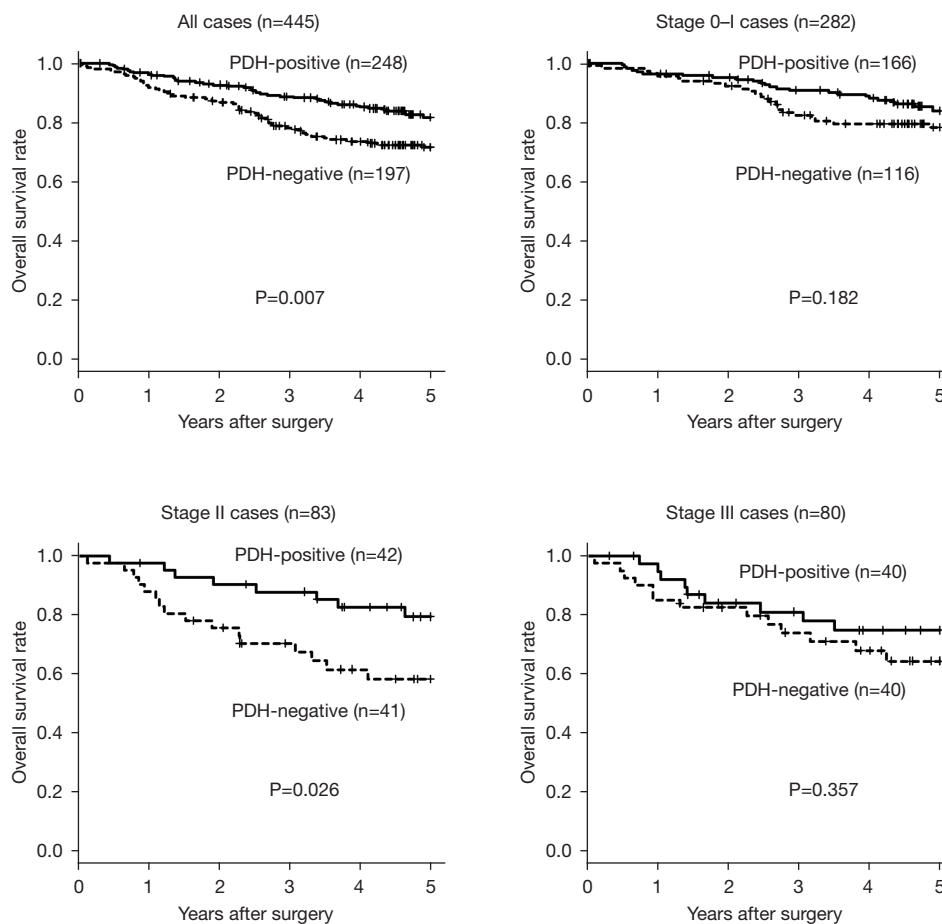
Figure 2 Relationship between overall survival rate and PDH-E1α expression. The 5-year overall survival rate in 445 patients with NSCLC. Patients showing negative PDH-E1α expression have significantly poorer survival rates (P=0.007) than those showing positive PDH-E1α expression. The PDH-E1α expression in associated with the pathological stage was evaluated. A significant difference in the association of survival rate and PDH-E1α expression in pathological stage II (P=0.026) was observed, but not for stages 0–I and III. PDH-E1α, pyruvate dehydrogenase E1α; NSCLC, non-small cell lung carcinoma.

(P=0.002), pleural invasion (P=0.002), and lymph node metastasis (P<0.001) were significantly correlated with a poor disease-free survival, while PDH-E1α negativity was not (P=0.068).

Discussion

Lung cancer is associated with a high morbidity and mortality rate worldwide; however, no reliable and independent prognostic predictor for NSCLC after curative surgery is available. PDH activity has been found to be associated with various cancers. However, few studies have evaluated the relationship between PDH-E1α expression and clinicopathological factors associated with NSCLC. In

this study, PDH-E1α expression in NSCLC was found to be significantly correlated with the presence of adenocarcinoma. It has been reported that histological adenocarcinoma type is associated with a higher oxygen-containing environment than that of squamous cell-type carcinoma in NSCLC (16). Normal cells obtain energy from glucose via mitochondrial oxidative phosphorylation under aerobic conditions (17). These findings suggest that the expression level of PDH-E1α might have been higher in adenocarcinoma than in squamous cell carcinoma due to the relatively higher oxygen levels in the adenocarcinoma environment.

A cell produces 34 molecules of adenosine triphosphate (ATP) from a single molecule of glucose through the glycolysis to TCA cycle and the electron transfer
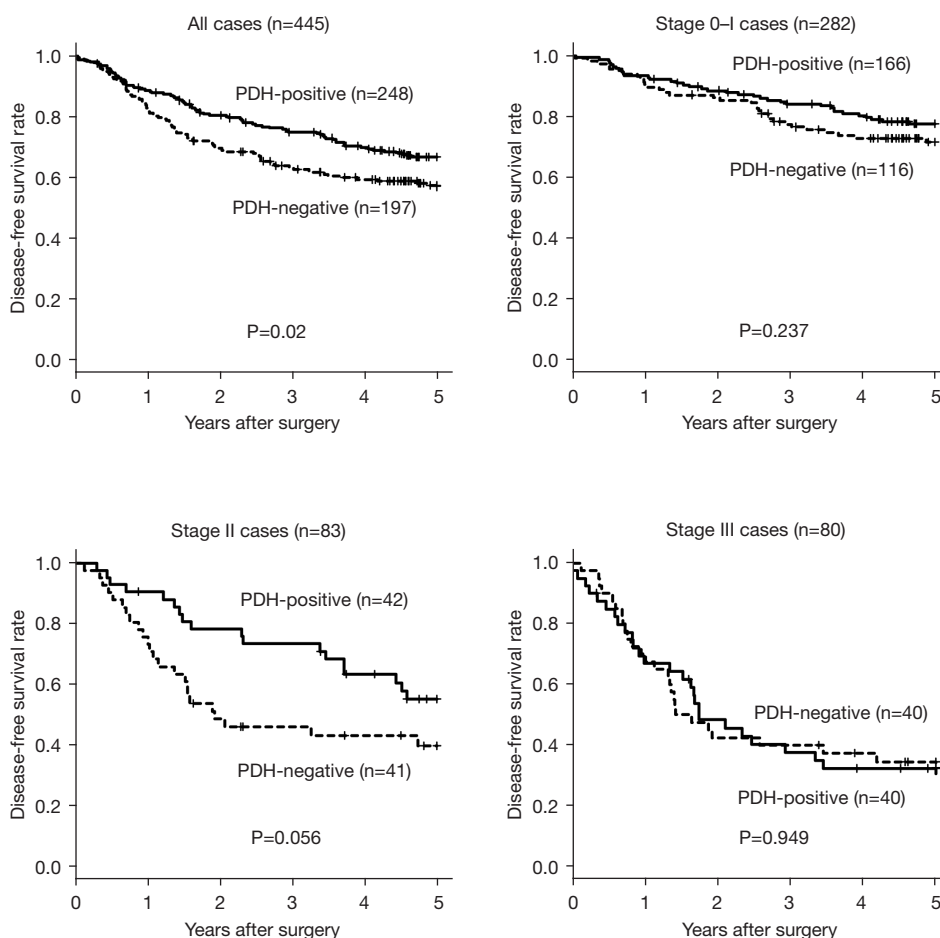
Figure 3 Relationship between disease-free survival rate and PDH-E1α expression. 5-year disease-free survival rate in 445 patients with NSCLC. Patients showing negative PDH expression had significantly poorer survival rates (P=0.02) than those showing positive PDH expression. No significant difference was found in the survival rate according to the PDH expression associated with pathological stage. PDH-E1α, pyruvate dehydrogenase E1α; NSCLC, non-small cell lung carcinoma.

system under normoxic conditions, called oxidative phosphorylation. On the other hand, a single molecule of glucose provides two molecules of ATP in a hypoxic environment, called anaerobic glycolysis. These two different metabolic pathways diverge at pyruvate. PDH-E1α catalyzes the conversion of pyruvate to acetyl-CoA, which enters into the TCA cycle, and PDH-E1α negativity induces anaerobic glycolysis. As anaerobic glycolysis is upregulated in cancer cells, extracellular acidosis is caused by the accumulation of lactate (18). Normal cells show a low tolerance to acidosis; however, cancer cells can readily adapt to acidosis via mutations such as in p53, and thereby continue to proliferate (19). Furthermore, when metastatic cancer cells proliferate by occluding the intravascular space, the tolerance to hypoxic environments and acidosis

is advantageous to cancer cells (20). These findings suggest that anaerobic glycolysis may be upregulated and PDH-E1α expression may be downregulated in cancer cells with malignancy potential.

Patients with NSCLC showing PDH-E1α expression were found to have significantly higher overall survival rates than those showing PDH-E1α-negative expression in pathological stage II. PDH-E1α expression may serve as an independent prognostic factor in patients with NSCLC treated with R0 resection, and was not significantly correlated with postoperative complications or administration of adjuvant chemotherapy. Low PDH-E1α levels in cancer cells are closely related to the malignancy potential of cancer cells, such as distant metastasis (20), suggesting that PDH-E1α may represent a reliable

Table 2 Univariate and multivariate analysis of 5-year overall survival of 445 patients with NSCLC

Variables	Subgroup	Number	Univariate analysis			Multivariate analysis		
			HR	95% CI	P value	HR	95% CI	P value
Sex	Female	155	4.99	2.66–9.37	<0.001	4.03	2.11–7.7	<0.001
	Male	290						
Age	<65	136	1.37	0.87–2.17	0.175			
	≥65	309						
Smoking	Yes	313	1.52	1.00–2.29	0.049	1.38	0.91–2.09	0.132
	No	132						
Histology	Adenocarcinoma	299	1.94	1.29–2.91	0.001	1.21	0.79–1.86	0.375
	Others	146						
Lymphatic invasion	Negative	305	1.78	1.18–2.67	0.006	1.22	0.77–1.94	0.394
	Positive	140						
Venous invasion	Negative	366	1.38	0.84–2.29	0.206			
	Positive	79						
Pleural invasion	Negative	331	1.94	1.27–2.94	0.002	1.5	0.94–2.38	0.086
	Positive	114						
Pathological T	1 or 2	384	1.82	1.1–3.01	0.02	1.1	0.64–1.88	0.729
	3 or 4	61						
Pathological N	0	346	1.74	1.12–2.7	0.014	1.22	0.76–1.96	0.419
	1 or 2	99						
Adjuvant chemotherapy	Yes	119	1.25	0.78–2.02	0.355			
	No	326						
Postoperative complications	Yes	63	1.39	0.72–2.68	0.323			
	No	382						
PDH-E1α expression	Negative	197	1.74	1.16–2.61	0.007	1.55	1.03–2.33	0.037
	Positive	248						

NSCLC, non-small cell lung carcinoma; CI, confidence interval; HR, hazard ratio; PDH–E1α, pyruvate dehydrogenase E1α.

prognostic predictor for patients with NSCLC after curative operation, especially at stage II.

However, PDH-E1α-negative expression had a significantly poorer survival rate in pathological stage II only, not in stages 0–I and III. This is probably because the expression of PDH-E1α indicates the potential of cancer malignancy. In patients with pathological stage 0–I NSCLC, the good effect of surgery for prognosis may be larger than the malignant potential of PDH negativity. On the other hand, the prognosis of patients with pathological stage IIIA NSCLC may have been significantly affected by

cancer progression rather than by the malignant potential of PDH-E1α negativity.

To the best of our knowledge, this is the first report to shows that PDH-E1α represents a reliable prognostic predictor for patients with NSCLC resected via curative operation. These findings suggest that PDH-E1α plays an important role in NSCLC development. PDH-E1α or PDK may serve as potential target in the treatment of NSCLC (21-23). Further investigation on the regulation of PDH-E1α expression may assist in identifying a promising therapeutic target for effective treating stage II NSCLC.

Table 3 Univariate and multivariate analysis of 5-year disease-free survival of 445 patients with NSCLC

Variables	Subgroup	Number	Univariate analysis			Multivariate analysis		
			HR	95% CI	P value	HR	95% CI	P value
Sex	Female	155	2.42	1.66–3.54	<0.001	1.86	1.25–2.76	0.002
	Male	290						
Age	<65	136	1.29	0.92–1.83	0.144			
	≥65	309						
Smoking	Yes	313	1.29	0.93–1.78	0.121			
	No	132						
Histology	Adenocarcinoma	299	1.42	1.04–1.95	0.029	0.84	0.59–1.19	0.318
	Others	146						
Lymphatic invasion	Negative	305	2.36	1.74–3.22	<0.001	1.29	0.9–1.85	0.168
	Positive	140						
Venous invasion	Negative	366	2.28	1.61–3.22	<0.001	1.21	0.83–1.77	0.332
	Positive	79						
Pleural invasion	Negative	331	2.53	1.84–3.46	<0.001	1.77	1.23–2.55	0.002
	Positive	114						
Pathological T	1 or 2	384	2.31	1.6–3.34	<0.001	1.45	0.95–2.2	0.087
	3 or 4	61						
Pathological N	0	346	3.1	2.26–4.27	<0.001	2.42	1.66–3.53	<0.001
	1 or 2	99						
Adjuvant chemotherapy	Yes	119	0.63	0.45–0.86	0.005	1.21	0.84–1.75	0.304
	No	326						
Postoperative complications	Yes	63	1.22	0.76–1.95	0.409			
	No	382						
PDH–E1α expression	Negative	197	1.44	1.06–1.95	0.021	1.34	0.98–1.83	0.068
	Positive	248						

NSCLC, non-small cell lung carcinoma; CI, confidence interval; HR, hazard ratio; PDH–E1α, pyruvate dehydrogenase E1α.

This study has some limitations. First, this is a retrospective study. It was not possible to analyze all factors in all patients, and some patients dropped out of the trial and could not be followed up upon. Second, we evaluated PDH-E1α expression only, but did not include all PDH subunits such as E1β, E2, or E3. In addition, PDH-E1α expression was evaluated only by immunohistochemistry. The accumulation of gene or mRNA data would be ideal for supporting the results of this study.

In conclusion, PDH-E1α represents a reliable prognostic predictor for patients with NSCLC undergoing curative resection. PDK may serve as a promising target for patients with NSCLC.

Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://dx.doi.org/10.21037/jtd-21-1463

Data Sharing Statement: Available at https://dx.doi.org/10.21037/jtd-21-1463

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/jtd-21-1463). 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Osaka City University Ethics Committee (Reference number 2019-006) and informed consent was obtained from all individual participants.

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