In Vitro Proton Magnetic Resonance Spectroscopic Lactate and Choline Measurements, ^{18}F-FDG Uptake, and Prognosis in Patients with Lung Adenocarcinoma

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It has been reported that ^{18}F-FDG uptake, lactate concentration, and choline concentration are good indicators of malignant grade in several different kinds of tumors. In this study, we investigated the correlation between ^{18}F-FDG uptake in ^{18}F-FDG PET imaging, lactate concentration and choline concentration measured by in vitro ^{1}H magnetic resonance spectroscopy (MRS), and survival probabilities in human lung adenocarcinoma. **Methods:** Nineteen patients with lung adenocarcinoma underwent ^{18}F-FDG PET before surgery. The ^{1}H MRS spectra were obtained in vitro from methanol–chloroform–water extracts of lung adenocarcinomas and normal lungs. The ratios of the lactate (R_{lac}) or choline (R_{cho}) concentration of lung adenocarcinoma to normal lung from the same patient were correlated with the mean standardized uptake value (SUV). The Kaplan–Meier life table method was used to analyze the relationship between ^{18}F-FDG uptake, R_{lac}, R_{cho}, and patient survival probabilities. **Results:** There was no significant correlation between mean SUV and R_{lac} or R_{cho} in patients with lung adenocarcinoma. An SUV $>$ 5 means poorer survival probabilities in patients with lung adenocarcinoma ($P = 0.004$). A higher R_{lac} probably indicates a trend for patients with lung adenocarcinoma to have poorer survival probabilities; however, R_{cho} is not an indicator of survival probability. ^{18}F-FDG uptake significantly correlated with cell differentiation ($P = 0.007$), whereas R_{lac} and R_{cho} had no correlation with it. **Conclusion:** No significant correlation was found between SUV and R_{lac} or R_{cho} in patients with lung adenocarcinoma. Compared with R_{lac} and R_{cho} measured by in vitro MRS, ^{18}F-FDG uptake is a better indicator of prognosis in patients with lung adenocarcinoma.

Key Words: ^{18}F-FDG; lung adenocarcinoma; magnetic resonance spectroscopy; lactate; choline; prognosis

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Warburg first discovered that tumors are characterized by abnormally increased glucose metabolism, with increased production of lactate (caused by glycolysis) (*1*). This finding has subsequently been used to clinical and research advantage.

After ^{18}F-FDG was introduced in clinical settings, PET with ^{18}F-FDG provided a means for the noninvasive quantitative assessment of tumor glucose metabolism in vivo (*2*). Recently, accumulative evidence has shown that ^{18}F-FDG uptake can serve not only as a good diagnostic tool for tumors but also as a good indicator of proliferative ability and prognosis in some tumors (*3,4*), particularly in lung cancer (*5–10*).

Lactate, as the end product of anaerobic glycolysis, may reflect tumor glucose metabolism by another aspect and can be detected noninvasively by magnetic resonance spectroscopy (MRS). It has been expected that hot spots on ^{18}F-FDG images could be matched by hot spots on lactate-concentration MRS images (*11*). Although, until now, there have been no conclusive results about the relationship between lactate concentration determined by MRS and tumor malignancy, some researchers have found that lactate concentration has prognostic value in patients with gliomas or cervical cancers (*12,13*).

Lung cancer has become the leading cause of cancer death in Japan and most Western counties. Therefore, the early and precise prediction of survival probabilities will facilitate more appropriate therapeutic planning for patients with lung cancer. Considering that increased glucose metabolism is an outstanding biochemical characteristic of cancer tissue, we tried to compare the prognostic significance of ^{18}F-FDG uptake by ^{18}F-FDG PET imaging (reflecting glucose metabolism) and lactate concentration by in vitro MRS (reflecting the end product of glycolysis) in this study. In addition, some reports found that choline concentration can indicate proliferative ability and prognosis in

some tumors (*14,15*), and choline PET has become a useful diagnostic tool (*16–19*) clinically. Therefore, we also compared the correlation between choline concentration and prognosis in patients with lung adenocarcinoma.

MATERIALS AND METHODS

Patients

Nineteen patients (8 male, 11 female; age range, 48–78 y; mean age, 64 y) participated in the study. All patients underwent a thoracotomy within 4 wk after their ^{18}F-FDG PET study. Final diagnoses were established histologically (via a thoracotomy) in all patients. The sizes of the tumors were determined from the resected specimens and ranged in diameter from 1.6 to 5.2 cm. None of the patients had insulin-dependent diabetes, and the serum glucose levels of all patients just before ^{18}F-FDG injection were less than 120 mg/dL. Informed consent was obtained from all patients participating in the study.

^{18}F-FDG PET

^{18}F-FDG PET was performed using a PET camera (Headtome IV; Shimazu) with a 10-cm axial field of view. The Headtome IV has 4 detector rings with 768 bismuth germanate crystals per ring. It uses direct and cross-plane coincidence detection to generate 14 slices per bed position. For the thorax, 2 bed positions (28 slices at 6.5-mm intervals) were obtained. Reconstruction in a 128 × 128 matrix using a Hann filter (0.5 cutoff) yielded 5-mm intrinsic resolution at the center. Transmission scans of all subjects were obtained before ^{18}F-FDG administration for attenuation correction using a ^{68}Ge ring source. A transmission scan was acquired for 10–20 min at each bed position, depending on the specific radioactivity of the ring sources at the time of the study, for at least 2 million counts per slice. Blood (1 mL) was drawn for the baseline blood glucose estimation, and the data were recorded. Immediately after the transmission scan, ^{18}F-FDG was administered intravenously. The average injected dose of ^{18}F-FDG was 185 MBq. After a 40-min uptake period, the patient was repositioned in the scanner. An emission scan was acquired for 10 min at each bed position, and the process took a total of 20 min.

For semiquantitative analysis of the ^{18}F-FDG uptake, regions of interest (ROIs) were manually defined on the transaxial tomograms that showed the highest uptake to be in the middle of the tumor. The ROIs placed on the lesions encompassed all pixels within that lesion that had uptake values of greater than 90% of the maximum uptake in that slice, and the average counted rate in each ROI was calculated. In patients in whom no nodules were detectable by PET, the ROI was extrapolated from chest CT scans. After correction for radioactive decay, we analyzed the ROIs by computing the standardized uptake values (SUVs) and PET counts/pixel/s × calibration factor/injected dose (MBq)/body weight, where the calibration factor = (MBq/mL)/(counts/pixel/s).

In Vitro ^{1}H MRS

Human lung cancer specimens were obtained from 19 patients undergoing scheduled surgical procedures. Noninvolved lung tissue was obtained from all patients at the same time. The surgically dissected lung tissue was immediately stored in 10% dimethyl sulfoxide solution at −20°C until use. Specimens ranged in weight from 20 to 230 mg.

The methanol–chloroform–water extracts were prepared according to previously described procedures (*20*), with some modification. Reagent-grade methanol and chloroform (4°C) in a ratio of 2:1 (v/v; 20 mL/g tissue) were added to the frozen, ground tissue. The tissue/solvent mixture was allowed to thaw before being transferred to polypropylene conical tubes. After approximately 15 min of contact with the first solvents, chloroform and distilled water were added to the samples in a ratio of 1:2 (6 mL/g of tissue) to form an emulsion. The samples were then centrifuged at 13,000 rpm for 20 min. The upper phase (methanol and water) was separated from the lower (organic) phase using a glass syringe. The residue from the first tissue extraction was then reextracted and pooled with the original extracted fractions. The total upper fractions were centrifuged at 3,000 rpm for 10 min, and 0.2 mL of a 1 mmol/L concentration of 3-(trimethylsily)propionic acid (TSP) was added as an external standard. The supernatant was then collected and lyophilized for 48 h.

After lyophilization, the dried extract samples were redissolved with 0.5 mL of D_2O in a 5-mm sample tube before the MRS analysis. The spectra were recorded with a 6.34-T spectrometer (JNM-EX270; JEOL) at 270.05 MHz for protons. The 1-dimensional proton spectra were acquired after 300 repetitions with acquisition of 16,000 data points. Quantification was performed by comparing the integrated TSP signal with the signal of the lactate and choline in the specimen spectrum after baseline correction. After the relative concentrations of lactate and choline were determined by spectra analysis, R_{lac} and R_{cho}—the ratios of the lactate or choline concentration of lung cancer to normal lung from the same patient—were calculated.

Statistical Analysis

All values are expressed as mean ± SD. The differences in ^{18}F-FDG uptake, R_{lac}, and R_{cho} between patients with different cell differentiation were determined using the independent 2-tailed Student *t* test. Probability values of less than 0.05 were considered statistically significant. Correlation was analyzed using the Pearson product moment test. Disease-free and overall survival probabilities were calculated with the Kaplan–Meier life table method. Differences between survival probabilities were analyzed using the log-rank test.

RESULTS

For the 19 patients evaluated in this study, the following data were measured and are summarized in Table 1: clinical, imaging, and follow-up.

A pair of typical spectra of the methanol–chloroform–water extracts from a poorly differentiated adenocarcinoma (PDA) and normal lung tissue (patient 17) are shown in Figure 1. Relative to the external standard TSP (0 ppm), the lactate peak and choline peak were located at 1.33 ppm and 3.22 ppm, respectively.

There was no correlation between SUV and R_{lac} in the 19 patients with lung adenocarcinoma ($r = 0.16$, not statistically significant) (Fig. 2A). There was also no correlation between R_{cho} and SUV (Fig. 2B).

The 19 patients were classified into 2 groups. Group A included bronchioloalveolar carcinoma (BAC) and well-differentiated adenocarcinoma (WDA), and group B included moderately differentiated adenocarcinoma (MDA) and PDA. For ^{18}F-FDG uptake, the mean value of group A (1.9 ± 0.7) was significantly lower than that of group B

TABLE 1
Clinical, Imaging, and Follow-up Patient Data

Patient no.	Age (y)	Sex	Histologic type	pStage	Size (cm)	MRS		^{18}F-FDG (SUV)	Postoperative recurrence	Survival interval (mo)		Status
						R_{lac}	R_{cho}			Disease-free	Overall	
1	60	F	BAC	IA	1.6	1.6	1.3	1.85	−	45	45	Alive
2	66	M	BAC	IB	4.0	1.1	1.0	2.14	−	34	34	Alive
3	59	F	BAC	IA	2.2	0.9	0.9	1.20	−	48	48	Alive
4	69	F	BAC	IB	3.8	1.2	2.6	2.78	−	37	37	Alive
5	76	F	BAC	IA	2.0	3.3	4.0	1.32	−	50	50	Alive
6	73	F	BAC	IA	2.8	1.1	2.0	2.31	−	31	31	Alive
7	61	F	WDA	IA	2.0	1.5	1.9	1.24	−	18	18	Alive
8	65	M	WDA	IA	2.8	0.5	1.9	1.79	−	34	34	Alive
9	48	F	WDA	IA	2.0	3.3	2.9	1.78	−	31	31	Alive
10	78	F	WDA	IA	2.0	2.1	3.0	1.21	−	23	23	Alive
11	65	F	WDA	IA	2.6	3.2	6.1	1.91	−	35	35	Alive
12	64	F	WDA	IA	3.0	0.6	2.4	3.25	−	2	2	Alive
13	74	M	MDA	IA	1.8	0.4	0.6	2.52	+	2	4	Deceased
14	64	M	MDA	IIIB	3.6	2.0	2.5	5.94	+	21	36	Deceased
15	69	M	MDA	IIIA	3.8	1.9	1.8	4.87	+	8	10	Deceased
16	60	F	MDA	IIIA	3.5	2.6	4.4	7.06	+	14	19	Deceased
17	50	M	PDA	IB	5.2	1.0	1.8	5.02	+	30	46	Deceased
18	54	M	PDA	IIIA	4.0	3.5	4.0	8.29	+	4	5	Deceased
19	73	M	PDA	IIA	2.7	1.1	3.0	8.05	+	38	45	Alive

pStage = pathologic stage; disease-free = time from date of operation until recurrence or the last follow-up date; overall = time from date of operation until death or the last follow-up date; BAC = bronchioloalveolar carcinoma; WDA = well-differentiated adenocarcinoma; MDA = moderately differentiated adenocarcinoma; PDA = poorly differentiated adenocarcinoma.

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(6.0 ± 2.0, $P = 0.007$) (Fig. 3A). There were no differences in R_{lac} and R_{cho} between groups A and B (Figs. 3B and 3C).

The Kaplan–Meier life table method was used to further analyze the relationship between ^{18}F-FDG uptake, R_{lac}, R_{cho}, and patient survival probabilities. According to the previous report (*8*), the patients were classified into 2 groups: a high-SUV group (SUV > 5) and a low-SUV group (SUV ≤ 5). The mean lactate and choline concentration ratios of all tumors were grouped into a high- and a low-lactate class or a high- and a low-choline class, compared with the median value of the overall data. A significant difference ($P = 0.004$) in survival probabilities between the high-SUV group and the low-SUV group in the disease-free survival analysis is shown in Figure 4A, and a marginally significant difference ($P = 0.058$) in the overall survival analysis is shown in Figure 4D. As shown in Figures 4B and 4E, there was a tendency toward a negative correlation between lactate concentration ratio and survival probabilities for patients with lung adenocarcinoma; however, neither of the results reached statistical significance in the disease-free or overall survival analysis ($P = 0.281$ and 0.178, respectively). No significant differences were found in either the disease-free or the overall survival probabilities in this study by choline concentration ratio grouping (Figs. 4C and 4F).

DISCUSSION

^{18}F-FDG PET imaging has been shown to be of value in the prognostic evaluation of some tumors (*3*,*4*). In lung cancer, prior studies have shown the importance of ^{18}F-FDG PET imaging in the assessment of aggressiveness, proliferative potential, grade of malignancy, and prognosis (*21*,*22*,*5*–*10*). A previous study even found that ^{18}F-FDG uptake is superior to pathologic stage in predicting relapses in patients with non–small cell lung cancer (*8*). The higher the SUV of the tumor, the worse the survival probabilities of the patients. In the present study we classified the patients into a high-SUV group and a low-SUV group, according to the former report (*8*). Compared with the low-SUV group, the high-SUV group had a worse outcome in this study, especially in the disease-free survival analysis ($P = 0.004$). In addition, the subgroup study showed that ^{18}F-FDG uptake is significantly different between patients with BAC or WDA and patients with MDA or PDA ($P = 0.007$). That finding demonstrates that ^{18}F-FDG uptake is of value in the prediction of malignancy in lung adenocarcinoma.

As the end product of anaerobic glycolysis, lactate is expected to reflect the glucose metabolism of the tumors. Because the lactate concentration can be detected in the MRS study, there are expected associations between the ^{18}F-FDG PET study and the MRS study, with the linkage being the detection of glycolysis (*11*). Recently, an in vivo MRS investigation of brain tumors found that the ratio of lactate concentration to *N*-acetyl aspartate was the strongest prognostic factor in that study. That ratio is a better indicator of survival than are tumor grade and patient age (*12*). This report is also in accordance with that of Walenta et al.

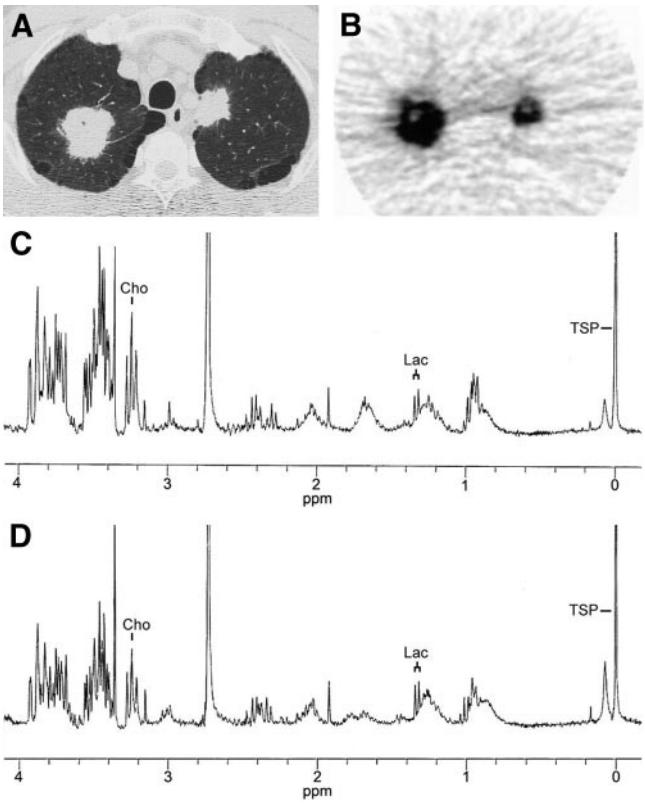

FIGURE 1. A 50-y-old man (patient 17) with PDA in both lungs. (A) CT shows that one tumor is in the right pulmonary apex and one is in the left pulmonary apex. (B) ^{18}F-FDG PET shows radioactive accumulation in the tumors. SUV is 5.02 (high-SUV group) for the lesion in the right lung. (C and D) MRS spectra for the lesion in the right lung (C) and for normal lung tissue from the same patient (D). The final calculated values were 1.0 (median, 1.9) for R_{lac} and 1.8 (median, 2.5) for R_{cho}. Lac = lactate; Cho = choline.

(*13*,*23*,*24*), who found that a higher lactate concentration means poorer survival probabilities in human cervical cancers and a higher incidence of metastasis in head and neck tumors. In the present study, although the survival analysis showed that survival was generally longer for patients with a lower R_{lac}, the difference did not reach statistical significance either in the disease-free or the overall survival analysis. Therefore, compared with the significant correlation between ^{18}F-FDG uptake and disease-free survival probabilities ($P = 0.004$), these results demonstrated that R_{lac} is not a good indicator of prognosis in patients with lung adenocarcinoma. In addition, no significant correlation was found between R_{lac} and ^{18}F-FDG uptake in this study. This discordance has various possible reasons. On the one hand, although lactate production is known to be higher in proliferating cells than in quiescent cells (*25*), some reports have suggested that ^{18}F-FDG uptake may not necessarily correlate with lactate production (*26*), because increased glucose use may be due to increased activity of the pentose phosphate shunt for increased DNA synthesis (*27*). On the other hand, because previous studies have shown that glucose transporter activity is the major rate-limiting step of ^{18}F-FDG uptake in some tumors (*28*,*29*), including non–small cell lung cancer (*30*), those previous findings may partially account for our current result of no correlation between ^{18}F-FDG uptake and lactate concentration. However, the underlying mechanism of this discordance still needs further investigation.

Choline-containing compounds are involved in both the synthesis and the degradation of cellular membranes. Because choline is characteristically elevated in some malignant tumors, its concentration as measured by MRS has been expected to be an indicator of grade of malignancy (*14*) and prognosis (*15*). However, there have been some conflicting reports regarding the relationship between the two. Tamiya et al. found that choline concentration can reflect proliferative ability in astrocytomas but cannot predict the survival probabilities of the patients (*31*). Another multicenter study also concluded that choline concentration cannot differentiate types of gliomas (*32*). In the present study, we found that R_{cho} was not associated with prognosis or with any of the other parameters tested, including ^{18}F-FDG uptake and cell differentiation.

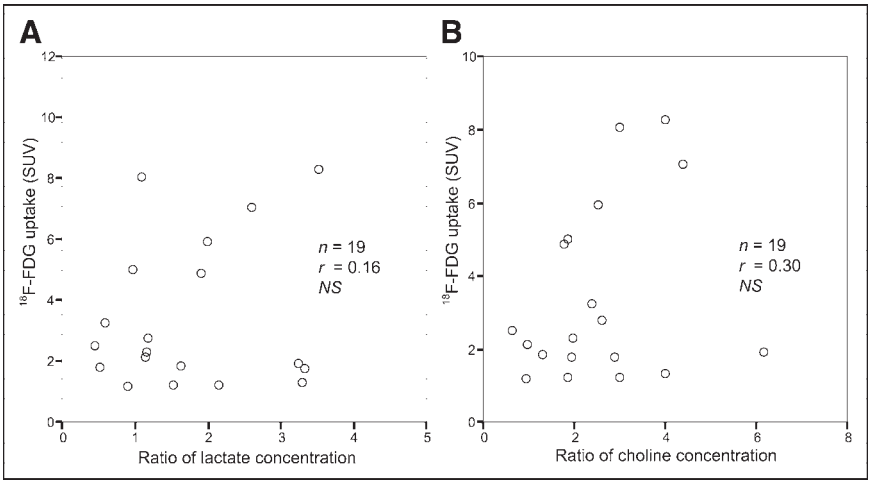

FIGURE 2. Relationship between ^{18}F-FDG uptake and R_{lac} (A) or R_{cho} (B) in lung adenocarcinoma. ^{18}F-FDG uptake showed no significant correlation with R_{lac} or R_{cho} in lung adenocarcinoma. NS = not statistically significant.

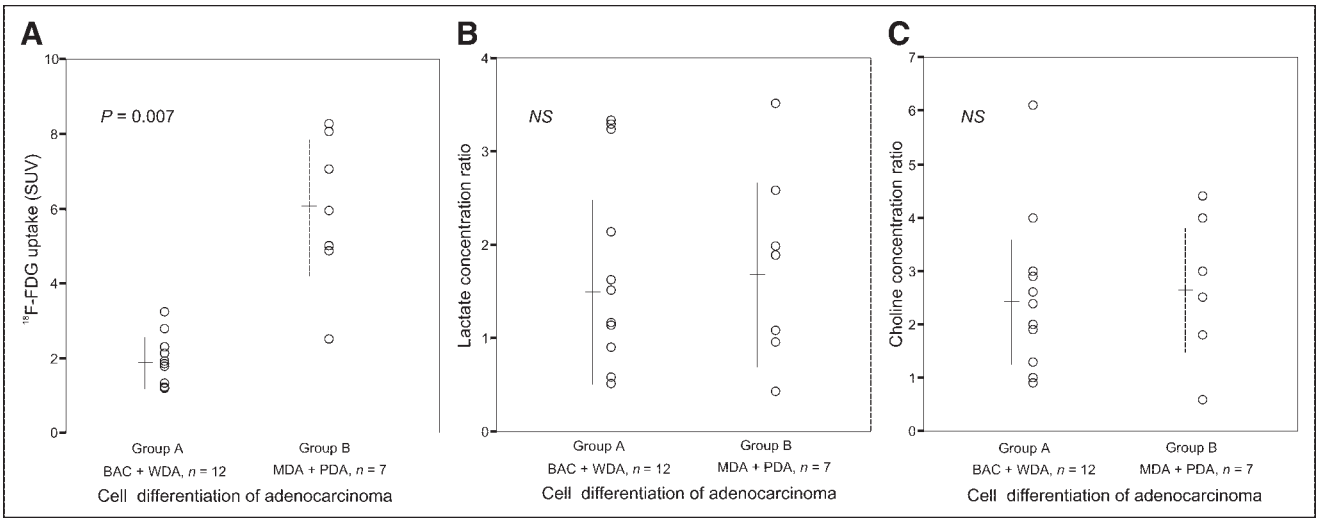

FIGURE 3. Relationship between cell differentiation and ^{18}F-FDG uptake, R_{lac}, and R_{cho} in lung adenocarcinoma. The mean SUV of group A (BAC + WDA) was significantly lower than that of group B (MDA + PDA) (A), whereas the mean R_{lac} (B) and R_{cho} (C) were not significantly different between the 2 groups. NS = not statistically significant.

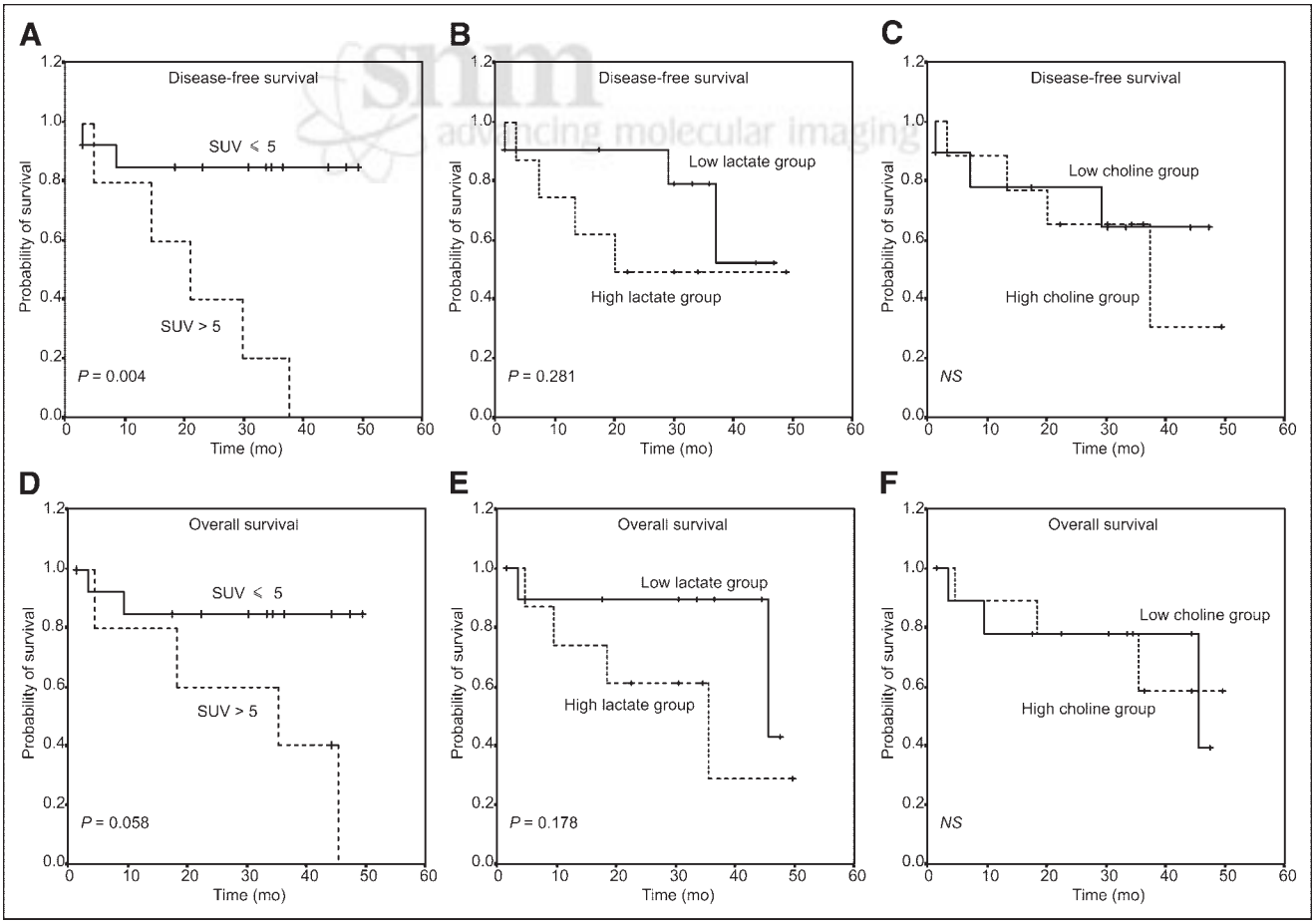

FIGURE 4. Kaplan–Meier plots showing disease-free (A–C) and overall (D–F) survival probabilities of patients with high or low SUV (A and D), high or low R_{lac} (B and E), and high or low R_{cho} (C and F). An SUV of 5 was used as cutoff value for ^{18}F-FDG uptake, and median levels were used as cutoff values for R_{lac} and R_{cho}. NS = not statistically significant.

On the whole, our results show that ^{18}F-FDG uptake is a better indicator of prognosis in patients with lung adenocarcinoma than are R_{lac} and R_{cho} measured by in vitro MRS. The results also show that ^{18}F-FDG uptake correlates significantly with cell differentiation ($P = 0.007$), whereas R_{lac} and R_{cho} have no correlation with it. To the best of our knowledge, there have been no previous reports on the relationship between lactate concentration, choline concentration, and prognosis in lung adenocarcinoma. Therefore, although the predictive value in lung adenocarcinoma is still obscure, lactate concentration still deserves attention, considering the importance of energy metabolism in tumor cells.

We realize that this study was limited by its small sample size—only 19 patients. Therefore, it was difficult to conclude whether R_{lac} can predict the outcome of lung adenocarcinoma in a larger number of patients. However, the preliminary results show that, compared with ^{18}F-FDG uptake, R_{lac} and R_{cho} are not good indicators of survival probability in lung adenocarcinoma. This study also did not include other types of lung cancer. Because different results have been obtained for some types of squamous cell carcinoma, further studies including patients with squamous cell carcinoma are needed.

CONCLUSION

Our results showed no significant correlation between SUV and R_{lac} or R_{cho} in patients with lung adenocarcinoma. Compared with the lactate and choline concentration ratios measured by in vitro MRS, ^{18}F-FDG uptake is a better indicator of prognosis in patients with lung adenocarcinoma.

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