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RESEARCH

MUC1 Expression in Pulmonary Metastatic Tumors: A Comparison of Primary Lung Cancer

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Abstract MUC1 expression has been described as a predictor for tumor progression and worsening of prognosis in various human neoplasms. However, little is known about the role of MUC1 expression in pulmonary metastatic tumors. The aim of this study is to examine the clinicopathological significance of MUC1 expression in pulmonary metastatic tumors (PMT). One hundred forty-seven patients with PMT who underwent ^{18}F-FDG PET before metastasectomy were included in this study. Tumor sections were stained by immunohistochemistry for MUC1, glucose transporter 1 (Glut1), hypoxia-inducible-1α (HIF-1α) and vascular endothelial growth factor (VEGF). ^{18}F-FDG uptake and the expression of these biomarkers were correlated in primary lung cancer. MUC1 expression pattern was classified into high-grade polarized expression (HP), low-grade polarized expression (LP), or depolarized expression (DP) group. Of 147 patients, HP, LP and DP group were 9 (6%), 114 (78%) and 24 (16%), respectively. The expression of Glut1, HIF-1αand VEGF, and ^{18}F-FDG uptake were significantly higher in DP group than HP or LP groups. MUC1 expression with HP and DP pattern was significantly higher in primary lung cancer than in PMT, whereas, MUC1 expression with LP pattern yielded a significantly high positive rate in PMT. LP group was recognized in the majority of patients with pulmonary metastatic adenocarcinoma, especially colon cancer, whereas, HP group was significantly low in pulmonary metastatic adenocarcinoma as compared with primary adenocarcinoma. Polarized MUC1 has a different expression pattern between primary and metastatic tumors with adenocarcinoma, and depolarized MUC1 is closely associated with glucose metabolism and hypoxia.

Keywords MUC1 · Pulmonary metastatic tumor · NSCLC · ^{18}F-FDG PET · Glut1 · Hypoxia

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Introduction

The impact of a strong expression of MUC1 mucin in various human neoplasms was repeatedly described as a predictor for tumor progression and worsening of prognosis [1–12]. Moreover, MUC1 has emerged as a target molecule in immunotherapy for various cancers [13]. As the mechanism of a target for cancer treatment, unmasked epitopes of MUC1 core protein expressed on tumor cells have been described to be able to elicit a strong antitumor immunity. But, the functional role of MUC1 expression is only partially elucidated.

Lung is one of the major metastatic sites of the neoplasm arising from other organs. Since it is sometimes difficult to

differentiate metastatic pulmonary nodule from primary lung cancer, pulmonary metastastasectomy has become an integral part of diagnosis and treatment if the primary malignancies outside the thorax are controlled. As pulmonary metastatic tumor (PMT) is a heterogenous group of tumors, there is only limited data about the comparison of molecular biology between pulmonary metastatic tumors and primary lung cancer.

Recently, several reports have documented that the over-expression of MUC1 has a crucial role on the cancer progression and metastasis, leading to poor outcome, in patients with non-small cell lung cancer (NSCLC) [3, 4, 13–16]. However, the precise expression profiles of MUC1 have not been yet determinate in PMT. Little is known about how the expression of MUC1 differs between primary lung cancer and PMT.

The usefulness of 2-[^{18}F]-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography (PET) can help predicting the therapeutic response and outcome in PMT patients [17]. The amount of ^{18}F-FDG uptake within tumor cells has been also documented to be determined by the presence of glucose metabolism [glucose transporter 1 (Glut1)], hypoxia [hypoxia-inducible factor-1α (HIF-1α)], and angiogenesis [vascular endothelial growth factor (VEGF)] [17, 18]. Recent experimental studies demonstrated that hypoxia enhances the expression of MUC1 through the direct regulation by HIF-1α in human cancer cell lines [19, 20]. Glut1 and VEGF could be regulated by HIF-1α-dependent way [17, 18], therefore, ^{18}F-FDG PET may be useful to evaluate whether hypoxia is associated with MUC1 expression in human neoplasm.

To elucidate the role of MUC1 expression in PMT, we conducted an immunohistochemical examination of MUC1 in patients with PMT, which was compared with primary lung cancer. In addition, MUC1 expression was correlated with Glut1, HIF-1α, VEGF, and ^{18}F-FDG uptake within tumor cells.

Material and Methods

Patients

We analyzed 170 consecutive patients who underwent ^{18}F-FDG PET and lung resection for pulmonary metastasis from extrathoracic malignancies at Shizuoka Cancer Center between April 2003 and May 2009. The patients who underwent PET study prior to pulmonary metastasectomy were included, and the patients with other malignancies and those who received induction chemotherapy or radiation before pulmonary metastasectomy were excluded from this study. Six patients who received induction chemotherapy or radiation therapy were excluded. Specimens of seven patients were not available. Ten patients were excluded from analysis because they did not have ^{18}F-FDG PET within 4 weeks before their pulmonary resection was performed. Thus, a total of 147 patients who underwent pulmonary metastasectomy were analyzed in the study. All patients were imaged on ^{18}F-FDG PET.

As a test group of pulmonary malignancy, we evaluated MUC1 expression and the biomarkers including ^{18}F-FDG PET in patients with NSCLC, as compared with PMT. One hundred thirty-three NSCLC patients were consecutively assigned in the study between October 2002 and May 2004, and ^{18}F-FDG PET was performed as part of the preoperative workup. These patients underwent surgical management, and the primary lesions were surgically resected. Finally, a total of 126 patients (81 men, 45 women) were eligible in the study. These 126 patients have no pulmonary metastatic tumors due to primary malignancies outside the thorax. Histologically, 82 patients had AC, 36 had SQC, and 8 had other histology. Of the total patients, 63, 25 and 38 had stage I, II and III tumors, respectively. The study protocol was approved by the institutional review board.

Immunohistochemical Staining

Immunohistochemical staining was performed according to the procedure described in the previous reports [3, 17, 18]. The following antibodies were used: a rabbit monoclonal antibody against MUC1 (Ma 552; Novocastra; 1:100 dilution); a rabbit polyclonal antibody against GLUT1 (AB15309, Abcam, Tokyo, Japan, 1:200 dilution); a mouse monoclonal antibody against HIF-1α (NB100-123, Novus Biologicals, Inc., Littleton, 1:50 dilution); a monoclonal antibody against VEGF (Immuno-Biological Laboratories Co.,Ltd., Japan, 1:300 dilution).

According to previous report [3], immunohistochemical analysis of MUC1 expression was evaluated. Firstly, staining density of MUC1 expression was classified into positive or negative, and if positive, each tumor cell was further classified according to the expression pattern into polarized or depolarized expression. According to the percentage of tumor cells showing polarized MUC1 expression and that with depolarized MUC1 expression, MUC1 expression was classified into the high-grade polarized (HP), the low-grade polarized (LP), or the depolarized (DP) group. The classification of MUC1 expression status is as follows: (i) HP when positive percentage of tumor cells with polarized MUC1 expression is more than 50% and positive percentage of tumor cells with depolarized MUC1 expression is less than 10%, (ii) LP when positive percentage of tumor cells with polarized MUC1 expression is less than 50% and positive percentage of tumor cells with depolarized MUC1 expression is less than 10%, (iii) DP when positive percentage of tumor cells with depolarized MUC1 expression is more than 10% regardless of positive percentage of with polarized MUC1 expression. According to

the definition, the patient with tumor showing no MUC1 expression was classified into the LP group.

The expression of Glut1 was considered positive if distinct membrane staining was present. Five fields (X400) were analyzed to determine the frequency of the HIF-1α stained nuclei. For Glut1 and HIF-1α, a semi-quantitative scoring method was used: 1=<10%, 2=10–25%, 3=25–50%, 4=51–75% and 5=>75% of cells positive. The tumors in which stained tumor cells made up more than 25% of the tumor were graded as positive. The expression of VEGF was quantitatively assessed according to the percentage of immunoreactive cells in the total of 1,000 neoplastic cells.

^{18}F-FDG PET Imaging

Patients fasted for at least 4 h before ^{18}F-FDG PET examination. Patients received an intravenous injection of 200–250 MBq of ^{8}F-FDG and then rested for approximately 1 h before undergoing imaging [17, 18]. Image acquisition was performed using an Advance NXi PET scanner and Discovery PET-CT scanner (GE Medical Systems, Milwaukee, WI, USA). Two-dimensional emission scanning was performed from the groin to the top of the skull. PET/CT image was independently reviewed by two experienced physicians. Acquired data were reconstructed by iterative ordered subset expectation maximization. To evaluate ^{18}F-FDG accumulation, the tumor was first examined visually, and then the peak standardized uptake value (SUV) of the entire tumor was determined. SUV_{max} was defined as the peak SUV value on one pixel with the highest counts within the region of interest (ROI). The ROI, measuring 3 cm in diameter, was set at the mediastinum at the level of the aortic arch and the mean SUV of the mediastinum was calculated. Finally, the T/M ratio, which is the ratio of the peak SUV of the tumor to the mean SUV of the mediastinum, was determined for each patient.

Statistical Analysis

Probability values of <0.05 indicated a statistically significant difference. Fisher's exact test was used to examine the association of two categorical variables. Correlation of different variables was analyzed using the nonparametric Spearman's rank test. Statistical analysis was performed using JMP 8 (SAS, Institute Inc., Cary, NC, USA) for Windows.

Results

Patient Characteristics

The median age of the patients was 64 years (range, 16–82 years). Eighty-one patients were men and 66 were women. The tumor size of resected metastatic tumors ranged from 5 to 68 mm (median, 14 mm). Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 0–1 in all patients. Seventy-five (51%) of 147 patients were smokers. Fifty-seven patients received adjuvant chemotherapy after pulmonary metastasectomy. The organ types of the primary site were as follows: 80 colon cancers, 7 breast cancers, 14 head and neck cancers, 12 soft-tissue sarcomas, 19 genital cancers, 12 gastrointestinal cancers and 3 other cancers. Forty (50%) of 80 patients with colon cancers have a primary site of rectum. Of 12 gastrointestinal cancers, 5 patients have esophageal cancer with SQC and 7 patients gastric cancer with AC. Of 12 sarcomas, 7 patients have osteosarcoma, 3 patients synovial sarcoma and 2 patients malignant fibrous histiocytoma. In NSCLC group, the median size of the resected lesions was 23 mm (range, 6 to 100 mm).

Immunohistochemical Analysis and ^{18}F-FDG PET Findings

Each protein revealed a profile pattern of the unique expression. The immunohistochemical staining was evaluated for the surgically resected 147 pulmonary metastatic lesions. Figure 1 represents the immunohistochemical staining of MUC1 expression. Of all 147 patients, HP, LP and DP group were 9 (6%), 114 (78%) and 24 (16%), respectively. The frequency of LP group was significantly higher than that of HP and LP groups ($p<0.0001$). Glut1 was detected in tumor cells and localized predominantly on their plasma membrane. A positive rate of Glut1 expression was recognized in 70%. A positive expression of HIF-1α was predominantly expressed in the cytoplasm with some nuclear staining, and was recognized in 70%. The staining pattern of VEGF was uniformly localized in the cytoplasm and/or membrane. The median rate of VEGF positivity was 22.0% (range, 2–76%), and the value of 22% was chosen as a cutoff point. High expression was recognized in 50%.

The mean values (mean and standard deviation) of T/M ratio in PMT and NSCLC were 3.25±0.22 (range, 0.95 to 9.43) and 5.96±0.38 (range, 0.8 to 24.0), respectively. The T/M ratio of PMT was significantly lower than that of NSCLC ($p<0.0001$). Of patients with NSCLC, The mean values of T/M ratio in AC and SQC were 4.93±0.51 (range, 0.8 to 21.5) and 7.32±0.73 (range, 2.4 to 24.0), respectively, demonstrating statistically significant difference. The T/M ratio of PMT was significantly lower than that of primary lung SQC, but was not than primary lung AC. The median value of T/M ratio in PMT was 3.0, and a median value of 3.0 was used as the cutoff T/M ratio in following analyses. The T/M ratio of more than 3.0 was defined as high expression.

Figure 2 shows the expression of these biomarkers and T/M ratio of ^{18}F-FDG uptake according to MUC1 expression. In PMT patients, the mean scoring of Glut1 and HIF-1α,

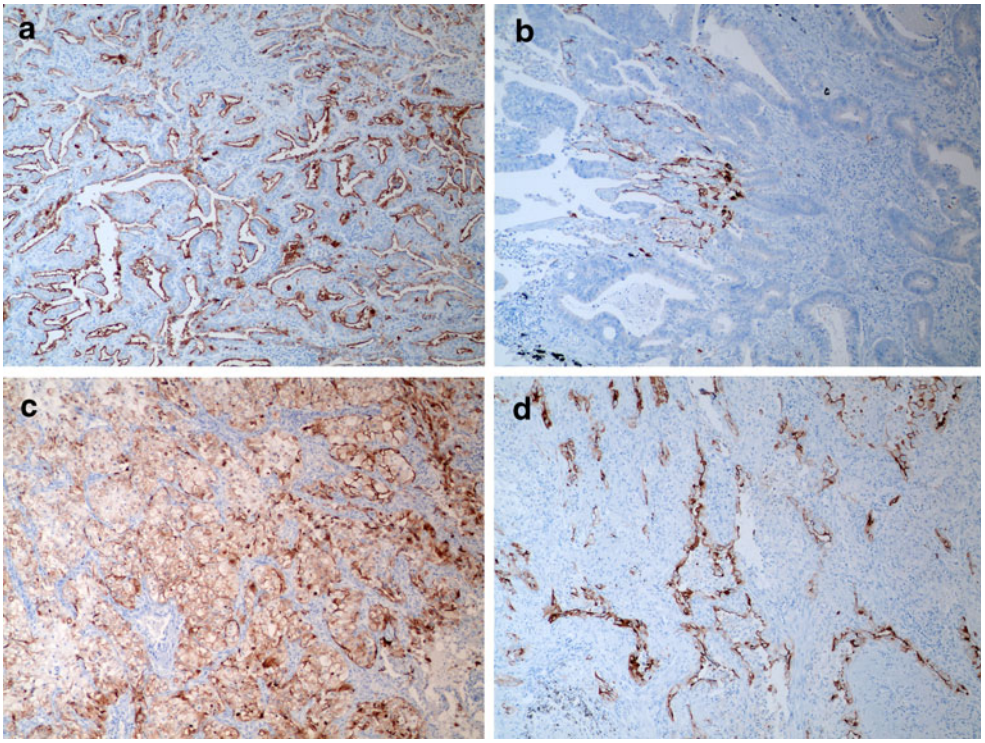

Fig. 1 Immunohistochemical staining of MUC1 expression in pulmonary metastatic tumors: **a** High-grade polarized expression (HP) pattern of MUC1 expression in breast cancer. **b** Low-grade polarized expression (LP) pattern of MUC1 expression in colon cancer. **c** Depolarized expression (DP) pattern of MUC1 in renal cell carcinoma. Immunohistochemical staining of MUC1 expression in primary lung cancer: **d** High-grade polarized expression (HP) pattern of MUC1 expression in pulmonary adenocarcinoma

VEGF positivity, and T/M ratio of ^{18}F-FDG uptake were significantly higher in DP group than HP or LP groups, demonstrating no significant difference between HP and LP groups (Fig. 2a). In patients with primary lung AC, the mean scoring of Glut1 and HIF-1α, VEGF positivity, and T/M ratio of ^{18}F-FDG uptake were significantly higher in LP group than DP group (Fig. 2b). No statistically significant difference in the uptake of ^{18}F-FDG and the meaning scoring of Glut1 and VEGF was observed between HP and LP groups, but uptake of ^{18}F-FDG, the mean scoring of Glut1 and VEGF positivity yielded a statistically significant difference between HP and DP groups. In patients with primary lung SQC, no statistically significant difference in these biomarkers was recognized between HP and LP, between LP and HP, and between HP and DP (Fig. 2c)

Relationship Between MUC1 Expression and Different Variables

The demographic result of the patients according to MUC1 expression is listed in Table 1. The frequency of young age, multiple metastases, large tumor size and a positive Glut1 expression was significantly higher in DP group than in HP group. A statistically significant difference in the age was observed between HP and LP group. The frequency of positive Glut1, HIF-1α and VEGF expression was significantly higher in DP group than in LP group.

We analyzed the expression of MUC1 according to histological types in PMT (Fig. 3a). One hundred and one patients had AC, 15 patients had SQC and 20 patients had sarcoma. In HP group, no significant difference in the positive rate of MUC1 expression was observed among AC, SQC and sarcoma patients. The positive rate of MUC1 expression with LP pattern was significantly higher in AC patients than in SQC patients. But, the positive rate with DP pattern was significantly lower in AC patients than in SQC patients.

According to the organ of the primary sites, the positive rate of MUC1 expression was examined (Fig. 3b). In colon cancer and soft-tissue sarcoma, the positive rate of MUC1 expression with LP pattern was significantly higher than that with HP or DP pattern. In head and neck cancer, MUC1 expression was significantly higher in LP pattern than in HP pattern. In genital cancer, MUC1 expression was significantly higher in DP pattern than HP pattern.

Next, we compared the expression of MUC1 between NSCLC and PMT (Fig. 3). In the analysis of total patients, the MUC1 expression with HP and DP pattern was significantly higher in NSCLC than in PMT, whereas, the MUC1 expression with LP pattern in PMT yielded a significantly high positive rate as compared with NSCLC (Fig. 3c). In AC patients, MUC1 expression with LP pattern was significantly higher in PMT than in NSCLC, whereas, the MUC1 expression with HP pattern in NSCLC yielded a significantly high positive rate as compared with PMT (Fig. 3d). In SQC patients, no significant difference in the positive rate of MUC1 expression was observed between NSCLC and PMT (Fig. 3e).

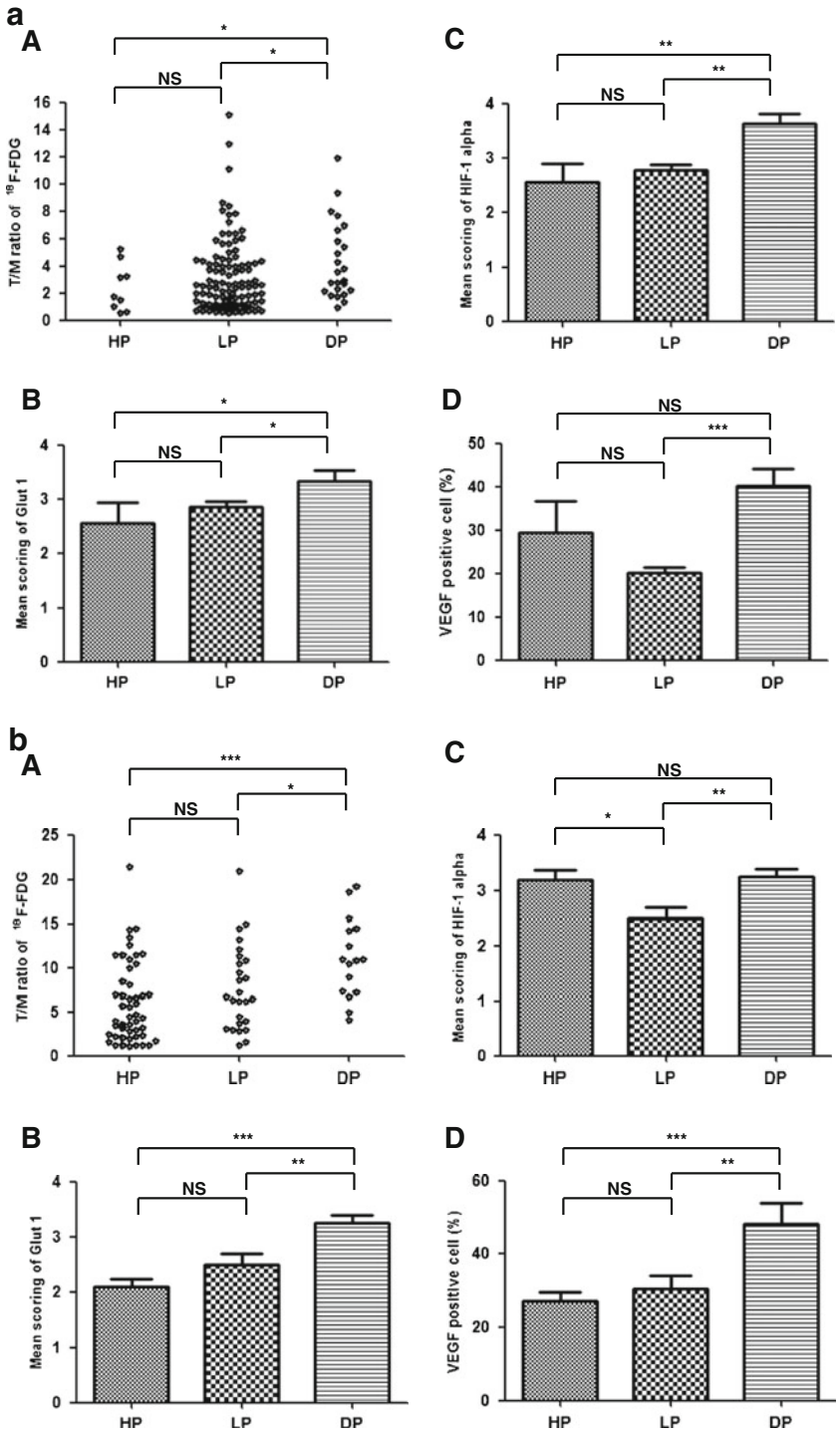

Fig. 2 Comparison of ^{18}F-FDG uptake and angiogenic markers according to MUC1 expression: HP, high-grade polarized expression; LP, low-grade polarized expression; DP, depolarized expression. **a** T/M ratio of ^{18}F-FDG uptake, the mean scoring of Glut1 and HIF-1α, and VEGF positivity of patients with pulmonary metastatic tumors according to MUC1 expression pattern. **b** T/M ratio of ^{18}F-FDG uptake, the mean scoring of Glut1 and HIF-1α, and VEGF positivity of patients with primary lung AC according to MUC1 expression pattern. *P* values indicate significance and were calculated using Fisher's exact test. **c** T/M ratio of ^{18}F-FDG uptake, the mean scoring of Glut1 and HIF-1α, and VEGF positivity of patients with primary lung SQC according to MUC1 expression pattern. *P* values indicate significance and were calculated using Fisher's exact test. *, $P<0.05$; **, $P<0.01$; ***, $P<0.001$. NS, not significant

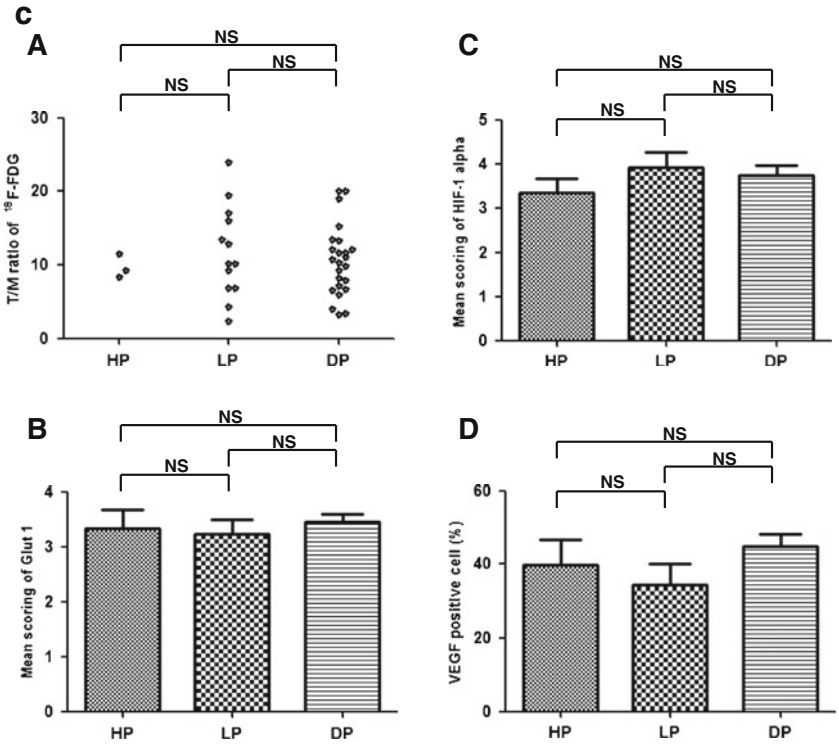

Fig. 2 (continued)

Discussion

This is a clinicopathological study to investigate the expression of MUC1 expression in patients with PMT as compared with NSCLC. MUC1 expression with LP pattern was observed in almost patients with PMT, especially colon cancer and soft-tissue sarcoma. In AC patients, the frequency of LP pattern was significantly higher in PMT tumors than in NSCLC, and MUC1 expression with HP pattern in NSCLC yielded a significantly high positive rate as compared with PMT. A high ^{18}F-FDG uptake in PMT was observed in DP pattern as compared to HP pattern, and the expression of Glut1 and HIF-1α were significantly higher in DP pattern

Table 1 Patient's demographics according to MUC1 expression

Different variables		Total (n=147)	HP (n=9)	LP (n=114)	DP (n=24)	p-value		
						HP/LP	HP/DP	LP/DP
Age	(≤ 65 / > 65 yr)	77 / 70	1 / 8	62 / 52	14 / 10	0.015	0.021	0.822
Gender	(Male / Female)	78 / 69	2 / 7	64 / 50	12 / 12	0.079	0.240	0.654
Smoking	(Yes / No)	76 / 71	2 / 7	63 / 51	11 / 13	0.082	0.263	0.500
PS	(0 / 1)	124 / 23	7 / 2	97 / 17	20 / 4	0.628	1.000	0.762
Tumor size	(≤ 15 / > 15 mm)	63 / 84	7 / 2	48 / 66	8 / 16	0.076	0.046	0.497
No. of meta	(Single / Multiple)	121 / 26	5 / 4	94 / 20	22 / 2	0.071	0.034	0.365
Adjuvant CTx	(Yes / No)	63 / 84	3 / 6	55 / 59	5 / 19	0.497	0.651	0.022
T/M ratio	(High / Low)	58 / 89	4 / 5	42 / 72	12 / 12	0.726	1.000	0.255
Glut 1	(Positive / Negative)	106 / 41	5 / 4	79 / 35	22 / 2	0.462	0.034	0.023
HIF-1α	(Positive / Negative)	103 / 44	6 / 3	75 / 39	22 / 2	1.000	0.110	0.012
VEGF	(Positive / Negative)	71 / 76	5 / 4	45 / 69	21 / 3	0.483	0.068	< 0.01

HP high-grade polarized expression; *LP* low-grade polarized expression; *DP* depolarized expression; *PS* performance status; *No. of meta* Number of resected metastases; *Adjuvant CTx* adjuvant chemotherapy; *Glut1* glucose transporter 1; *HIF-1α* hypoxia inducible factor-1 alpha; *VEGF* vascular endothelial growth factor; *HP/LP* statistical comparison of HP and LP; *HP/DP* statistical comparison of HP and DP; *DP/LP* statistical comparison of DP and LP

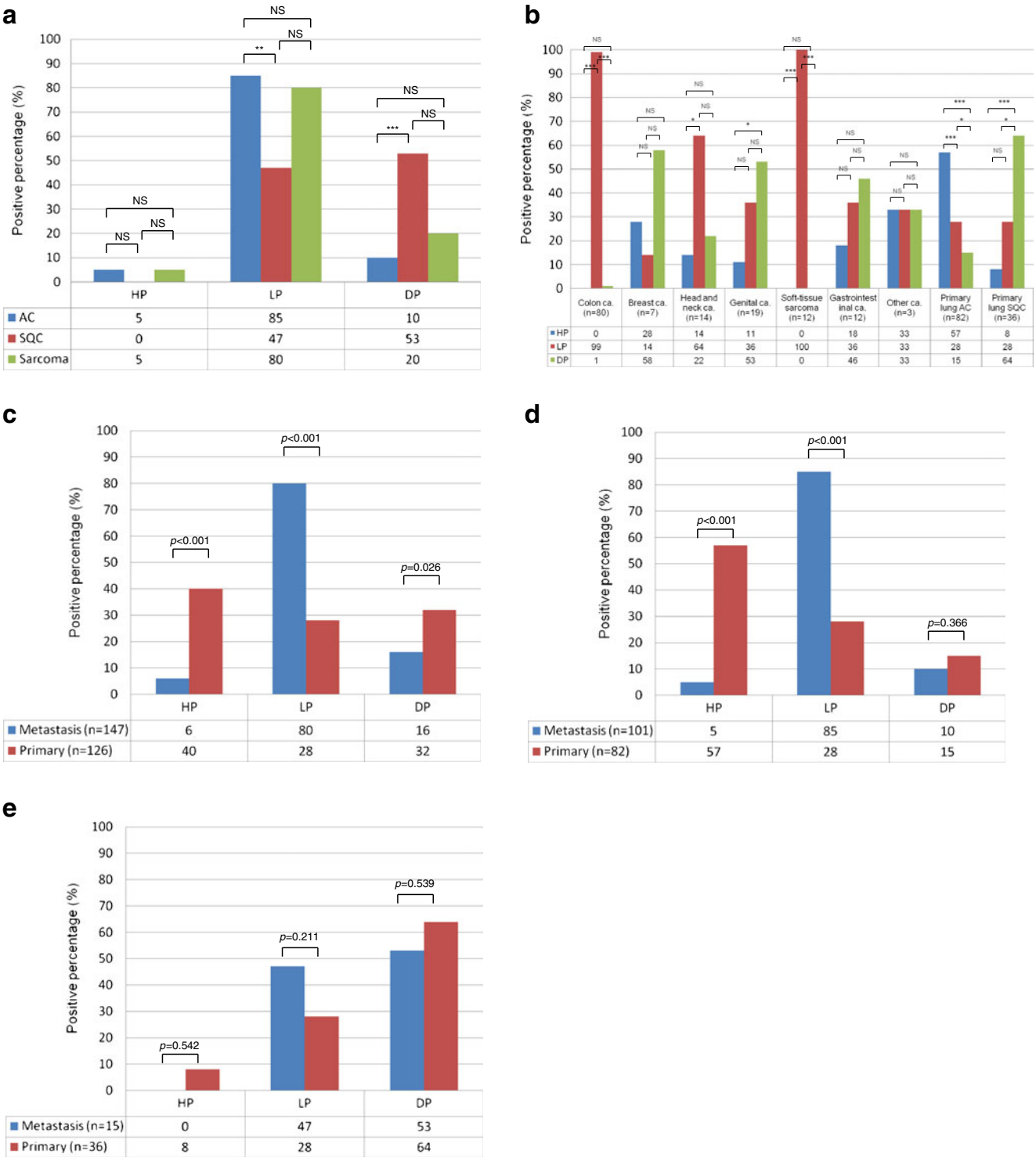

Fig. 3 Comparison of MUC expression according to primary sites and histological types: HP, high-grade polarized expression; LP, low-grade polarized expression; DP, depolarized expression; AC, adenocarcinoma; SQC, squamous cell carcinoma. **a** MUC1 expression according to histological types in pulmonary metastatic tumors. **b** Positive rate of MUC1 expression according to the organ of the primary sites. Comparison of MUC1 expression between primary lung cancer and pulmonary metastatic tumors in total patients (**c**), AC patients (**d**) and SQC patients (**e**). *P* values indicate significance and were calculated using Fisher's exact test. *, $P<0.05$; **, $P<0.01$; ***, $P<0.001$. NS, not significant

than in HP pattern. This was corresponding to the results of pulmonary lung AC.

MUC1 is a transmembrane mucin consisting of a heavily *O*-glycosylated excellilar domain, a transmembrane domain

and a cytoplasmic tail of 72 amino acids [1]. Recently, several reports have documented that MUC1 expression is correlated with tumor differentiation and postoperative survival in patients with NSCLC [4, 14–16], and Nagai et al has described that depolarized MUC1 expression was a significant and independent prognostic factor to predict poor postoperative prognosis in patients with pulmonary adenocarcinoma and LP or DP expression was mostly observed in moderately to poorly differentiated adenocarcinoma patients [3]. Nagai et al conducted a more detailed MUC1 status classification (HP, LP and DP) for the immunohistochemical evaluation of MUC1 expression in pulmonary tumors [3]. In previous literatures, the immunohistochemical analyses of MUC1 expression were different among the primary tumors and the studies, and the methods used in the studies also have a different technique [4–12]. To analyze the MUC1 expression of pulmonary tumors, therefore, we selected the expression analysis of MUC1 according to Nagai's study [3]. In this study, we could directly compare the expression of MUC1 between NSCLC and PMT.

In our study, low-grade polarized MUC1 expression was observed in the majority of patients with PMT, especially adenocarcinoma such as colon cancer or soft-tissue sarcoma. On the other hand, the frequency of high-grade polarized MUC1 expression was significantly low in pulmonary metastatic adenocarcinoma as compared with primary adenocarcinoma. Only small number of patients with PMT showed the expression pattern of high-grade polarized MUC1, and depolarized MUC1 expression was mainly observed in patients with SQC or genital cancers. In patients with AC as pulmonary nodules, the primary sites are sometimes difficult to differentiate between primary lung cancer and extrathoracic tumor. However, our results suggest that polarized MUC1 (HP or LP pattern) has a markedly different expression pattern between primary and metastatic pulmonary tumors with a histological type of AC. In patients with SQC as pulmonary nodules, whereas, it is difficult to differentiate NSCLC from PMT, because the expression profile of MUC1 was similar among these groups. In addition, ^{18}F-FDG uptake within tumor cells tended to increase from HP, LP to DP pattern, and the expression of Glut1 and HIF-1α was also significantly higher in DP pattern than in HP or LP pattern. Hypoxia has been documented to enhance MUC1 expression in human cancer cell lines, and the present study suggested that hypoxia and glucose metabolism were closely associated with the expression of depolarized MUC1 as compared with that of polarized MUC1. In clinical practice, ^{18}F-FDG PET may be effective for differentiating between polarized MUC1 and depolarized MUC1 expression tumors. However, ^{18}F-FDG PET was not useful for differentiating between HP and LP pattern of MUC1 expression in PMT patients.

MUC1 core protein may be a useful target molecule for immunotherapy in breast cancer, lung cancer and other malignancies expressing MUC1 [21, 22]. MUC1-targeted immunotherapy may be appropriate for such patients as postoperative adjuvant therapy. However, it remains unclear whether MUC1 expression is associated with postoperative outcome in patients with PMT. If not investigate the relationship between MUC1 expression and prognosis, it seems to be difficult to speculate the possibility of a MUC1-targeted immunotherapy after pulmonary metastasectomy in patients with PMT.

In conclusion, polarized MUC1 (HP or LP pattern) had a markedly different expression pattern between primary and metastatic pulmonary tumors with a histology of AC, and depolarized MUC1 was closely associated with glucose metabolism and hypoxia. In addition, ^{18}F-FDG PET may be effective for differentiating between polarized MUC1 and depolarized MUC1 expression tumors. Further study is warranted for investigating the possibility of a MUC1-targeted immunotherapy as a postoperative adjuvant chemotherapy after pulmonary metastasectomy.

Conflicts of Interest Statement We, all authors, have no financial or personal relationships with other people or organizations that could inappropriately influence our work.

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